Insulin

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AND THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH

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The personality of Frederick Grant Banting made such a lasting impression upon those of us who knew him well that it is difficult to realize that it is more than eleven years since he left us. These memories, obtained from many points of vantage, will all be clear and in the forefront of our minds. Some of you knew him when he was fulfilling the promise of his earlier years. A few of us knew him before he became Canada's most famous scientific son. I have my own vivid memories, particularly of our work together in the spring, summer and autumn of 1921.

There are two very high peaks which feature the brilliant record of Banting's achievements. The first was in that intensive period preceding the discovery of insulin, when all considerations were laid aside except those which advanced the research. The second came just before and in the early phases of the Second Great War when he gave inspired leadership in the effort to develop the full potential of Canadian medical research for the emergency. His courage, vigor and perseverance were abundantly demonstrated on both these occasions. In the latter, maturity and administrative ability had been added to his younger qualities of greatness. Last year I had the honor of unveiling a bust to Fred Banting which now stands in our Simcoe Hall. The sculptress, Miss Frances Loring, captured and preserved for posterity those characteristics of youthful vigor and mature strength combined with complete courage and firmness of purpose which made Banting the great man he was.

When the Program Committee of our Council invited me to give this lecture I did not look far for a title. A perfectly objective approach to the historical aspects of this subject is obviously impossible for me. It has been attempted in our columns by others with, as would be expected, different degrees of success. There have been a few interesting statements about the

early development of insulin which I completely fail to recognize. Objective descriptions are, of course, invaluable and there are some who are particularly well qualified to make them in this field. The names of Dr. Elliott P. Joslin in this country, Sir Henry Dale in England, and Dr. Bernardo Houssay in the Argentine come to my mind. I will not attempt to select any names from an even younger group, but there are many in this Association who are interested and well informed on these matters.

The facts are simple and straightforward. The young surgeon formulated an hypothesis which was vital to his initiation of the work and it thus completely fulfilled its function. He obtained permission to explore this hypothesis in the Physiological Laboratory of his Alma Mater and he received some excellent general advice from the Head of the Department. The second working hypothesis was that an internal secretion of the pancreas existed and that it could be captured. This one Banting and I shared, and in its exploration we invested our time and energy. We formed a partnership which was based on the new knowledge and experience which we gained together. We had no stipends, but the facilities of Professor Macleod's deserted department were at our disposal. We worked completely alone during the four summer months of 1921 without any verbal or written advice from any senior investigator and until well after the salient facts, consistent dramatic lowering of blood and urinary sugars and complete recovery of our moribund depancreatized dogs, had been repeatedly demonstrated.

In the spring of 1923 the first recognition of our work came with the award of The Reeve Prize of our Faculty of Medicine to Banting and myself for the discovery of insulin. The prize was $50.00 and was "awarded annually on the basis of a published report of the best scientific research accomplished in any department of the Faculty of Medicine by a research fellow or junior member of the staff." Later in the same year The Banting and Best Act of The Ontario Legislature, creating a Chair of Medical Research with the same names, was passed.

Banting and I presented our work to the Medical Faculty at a departmental seminar in the autumn of 1921, and our findings were later published in two papers under our names in the *Journal of Laboratory and Clinical Medicine*. These papers give the first detailed account of our isolation of insulin. We were given the impression that a member's name was necessary for the acceptance of a paper to be read at the meeting of The American Physiological Society, and for this reason Professor Macleod's was added to the preliminary paper presented in December 1921. Banting and I always hoped that our article on "The Internal Secretion of the Pancreas," which appeared in the February 1922 issue of the *Journal of Laboratory and Clinical Medicine*[1] and which we wrote for and presented to our Medical Faculty on November 14, 1921, would be universally accepted for what it in fact was, the original record of our work. The paper which bore, in addition, the name of the Head of the Department was a summary of the longer one. We prepared it later, but it appeared in print first.[2]

Banting generously stressed our fraternal partnership and the interdependence of the surgical and biochemical techniques in several public announcements and in unpublished letters. When Professor Macleod asked me if I would like to volunteer for the work with Banting, I was not actually a medical student. Rather, after five years of University study, and a year in the Canadian Army, I was a very recent graduate in the Arts Course of Physiology and Biochemistry. I was deeply interested in Physiology, and for family reasons particularly interested in diabetes. I had been a part-time research worker on diabetes and a demonstrator in Physiology to the medical students during 1920-21. I was registered for an M.A. in Physiology during the year Banting and I worked together and was awarded this degree in June 1922. In September 1922, sixteen months after Banting and I began our work, I decided to proceed toward an M.D. rather than a Ph.D. degree and registered for the first time in the Medical Faculty of the University of Toronto.

As the representative of the staff of the Department of Physiology when insulin was discovered, and of the staff of the Department created in 1923 by The Banting and Best Act of The Ontario Provincial Legislature, I have a sensation of giving an account of my stewardship —not only to the present membership of the American Diabetes Association, but to some who are no longer with us.

THE SOURCE OF INSULIN

A good starting point for a discussion of insulin is the Islands of Langerhans. After a brief historical review I will select, for emphasis, certain aspects of this interesting subject. In 1869, in the introduction to his article entitled "The Microscopic Anatomy of the Pancreas,"[3] Paul Langerhans wrote: "There is indeed hardly another organ in which there is such glaring contrast between the brilliant results of physiological research and the

complete darkness in the realm of anatomical knowledge." The pancreas was known merely as a racemose gland in spite of the very early work of the Dutch investigator Regner de Graaf[4] and Claude Bernard's demonstration[5] that its secretion played a vital role in the digestion of carbohydrates, proteins and fats. Langerhans was a very young man, 22 years old, when he published this, the third of his scientific papers, and he was appropriately modest. He wrote: "I can describe at most a few isolated observations which suggest a much more complicated structure of the pancreas than hitherto accepted." In introducing the newly recognized bodies he stated: "The cell is a small irregularly polygonal structure. . . . The cells lie together, generally in considerable numbers, diffusely scattered in the parenchyma of the gland." There is no suggestion anywhere in this article that Langerhans had any idea of the physiological significance of his cells, but the more experienced histologist Laguesse did suggest an endocrine role. "Dans le pancreas d'un homme adulte (supplicié) je retrouve ces îlots très nombreux et volumineux (je les désignerai provisoirement sous le nom d'îlots de Langerhans)." Thus we read the thoughtful words which immortalized Langerhans. They appear in one of a series of short articles by Laguesse in *Mémoires de la Société de Biologie*, 1893.[6]

In 1907 M. A. Lane,[7] a pupil of R. R. Bensley's, made an important advance in knowledge of the islands. He developed more definite procedures for the differentiation of the alpha and beta cells. The granules of the alpha cells are relatively large and have large spherical nuclei with little chromatin. The granules are precipitated by 70 per cent alcohol. The granules of the beta cells are soluble in this concentration of alcohol but are precipitated by aqueous chrome sublimate. They are much more numerous and considerably smaller than those of the alpha cells and contain higher concentrations of chromatin.

Professor R. R. Bensley, a graduate from Toronto in 1892 who has spent most of his active life in the U.S.A., has perhaps more than any other person of his generation informed us regarding the minute structure and interrelationship of the cells in the islands of Langerhans. His work widened and strengthened the foundation upon which our present conceptions are based. One of Bensley's contributions was the clear demonstration of a system of fine anastomosing tubules about the pancreatic duct which are in continuity with the islands Langerhans. Figure 1, from his work, illustrates this relationship in a drawing and Figure 2 shows a photomicrograph of a preparation which demonstrates the

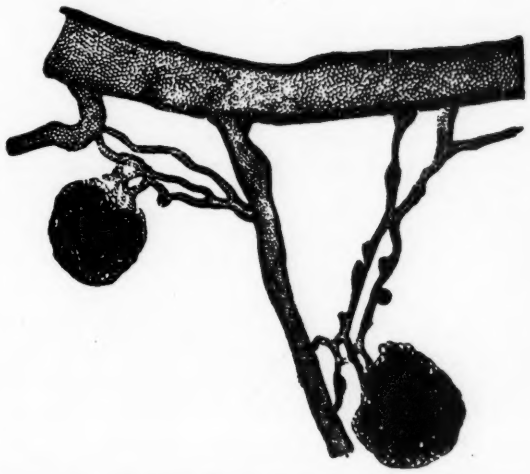


FIGURE 1 Diagrammatic representation of the intimate relationship between islet tissue and ducts in the pancreas of a guinea pig. × 70. (Redrawn after Bensley; from Maximow and Bloom: Textbook of Histology, 5th Edition, W. B. Saunders Company, Philadelphia, 1948, p.448.) See Figure 2 for appearance in microsections.

duct-islet association with particular clarity. Mr. William Wilson (our senior histological technician) who made many of the preparations I am using, suggested that the publication of the drawing and this photomicrograph in the same article would be of interest. In Figure 3, granules staining in the same way as those in beta cells are shown within duct cells. This section is from one of Dr. R. E. Haist's partially depancreatized rats which was to secure his reaction to the present situation. He answered promptly in his own firm hand:

"I am afraid that my knowledge of recent developments is too meagre to give you much help . . . The record of the medical profession in the management of diabetes, both pre-insulin and post-insulin, has been a magnificent one and has my enthusiastic admiration. In the fundamental sciences, however, the tendency to a narrow point of view has been ever manifest. The preoccupation at the present time with the alloxan phenomenon is, to my mind, an evidence of this since most modern workers in this field seem to be unaware that in the pre-insulin era cases of diabetes of the greatest severity, proceeding rapidly to a fatal issue, occurred in which no indication of histological changes in the islands of Langerhans or in the pancreas as a whole could be discovered. I investigated several such cases myself with the most advanced techniques. I examined these pancreases with the full cooperation of the physician as to promptness of autopsy and methods of preparation. In that period the pathologist felt a sort of compulsion to adapt his findings to a popular theory

and this compulsion spoilt his objectivity. In those cases where reduction in number or size of the Islands was not reported, obviously the pathologist was at his wit's end to explain the disease. I think that it is important that workers in the fundamental sciences who are engaged in this field should be made to realize that, while plus or minus insulin is an important factor, the situation is far more complex. The recent experiences with ACTH and cortisone help us to appreciate these facts, although I am sorry to say that the medical profession has not exercised the restraint and caution in the use of these hormones which was imposed in the case of insulin by the dramatic results of over or under dosage."

I will bring to your attention today some evidence supporting, in a general way, Professor Bensley's view. There are many facts, as he states, which emphasize the complexity of clinical diabetes. As a physiologist one could not, of course, accept the normal appearance of a gland as a complete proof of normal function. The histologist and the physiologist are not now, as in the past, commonly integrated in a single individual, but they can work together most profitably. Using appropriate stains, my colleagues Drs. Hartroft and Wrenshall find that the granule count in the cells may frequently run parallel to the amount of insulin extractable. Indeed, this had been observed in the earlier work on diet and insulin content of pancreas which Haist and I discussed some years ago. Similarly, in metadiabetes produced in dogs by purified growth hormone or by alloxan, the histologist can predict with reasonable accuracy what the insulin content will prove to be. This is also true in "growth onset" type of human diabetes, where the lesions in the cells are always advanced and the insulin content is consistently low. But difficulties were encountered when the pancreas of "maturity onset" diabetics was studied, and the correlation of granule counts and insulin content was not nearly as satisfactory as in cases exemplifying other types of diabetes. The basic cause of this situation is, quite probably, that an extensive depletion of granules becomes obvious and unmistakable, but when the decrease is slight various other factors affect the picture and it is impossible for the histologist always to make an accurate interpretation.

It is important and interesting to ask: "In how many diabetic patients is there no evidence of any abnormality in the manufacture or liberation of insulin?" Professor Bensley had referred to the fact that he was unable to detect any islet cell abnormalities in some diabetic patients at autopsy. Shields Warren[8] states that 26 per cent of the autopsies in his series of diabetics revealed essentially normal islets. Wrenshall, Bogoch and Ritchie[9] found the average insulin content of the pancreas of "maturity onset" diabetics approximately half that of nondiabetics. Based on units of insulin per gram of pancreas, 6.8 per cent of the diabetics had values falling *above* the average of nondiabetics. Based on units of insulin per square meter of surface, 3.4 per cent had values above the nondiabetic average. The number of cases of "maturity onset" diabetics falling within the standard deviation range of nondiabetic controls was 32 per cent based on units per gram of pancreas, or 21 per cent based on units per square meter of body surface. Three diabetics out of 59 had more total insulin in their pancreas than the average nondiabetic. Twelve had values falling within the range of standard error of the nondiabetics.

We are interested in the histological appearance of the islets and in their insulin content, but the deduction

FIGURE 2 Normal islet from pancreas of rat. Two small ducts in cross section appear surrounded by islet cells. The beta granules are stained deep purple, while the cytoplasm of the alpha cells is green. Wilson modification of Gomori's aldehydefuchsin stain. ×1000.

FIGURE 3 Granules are visible in the cytoplasm of some of the epithelial cells composing the duct in the central portion of the field. The tinctorial reaction and morphology of these granules are similar to those in the adjacent beta cells. The field shows a portion of an islet in the residual part of the pancreas of a rat which had been subjected to partial pancreatectomy by Professor R. E. Haist. Gomori's chromium haematoxylin and phloxine stain. ×1000.

FIGURE 4 Islet of Langerhans in a normal guinea pig. Gomori's chromium haemotoxylin and phloxine stain. The peripheral arrangement of the alpha cells (red) around the more central beta cells (blue) is a frequent, but not constant, feature of the islets in this species. ×700.

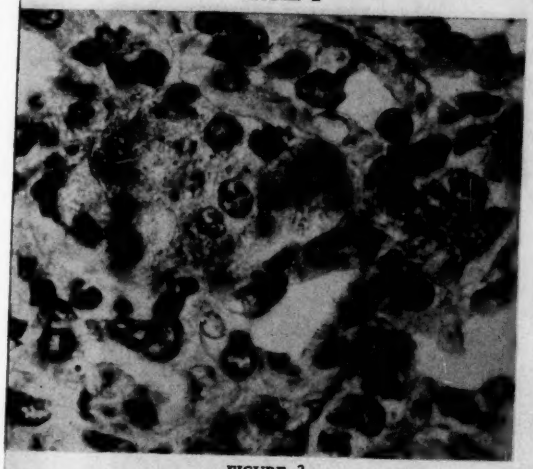
FIGURE 5 A small group of islet cells are shown embedded in waves of fibrous tissue following ligation of the pancreatic duct in a dog by Dr. J. M. Adams. Granulation in the beta cells (blue-gray) is sparser here than in the alpha cells (red). Gomori's chromium haematoxylin and phloxine stain. ×1000.

FIGURE 6 Glycogen (red) may be seen in the cytoplasm of the epithelial cells which form the walls of the ductules in the pancreas of this dog which became spontaneously diabetic. Very few islets could be found in sections of this pancreas which Dr. G. A. Wrenshall found contained little extractable insulin. Best's carmine stain and light green. ×1000.

FIGURE 7 Granules in the beta cells of this islet from a normal man are stained deep purple. The granules may frequently lie massed along that boundary of the cell which abuts on a sinusoid. Wilson modification of Gomori's aldehyde-fuchsin stain. ×1000.

FIGURE 2

FIGURE 5



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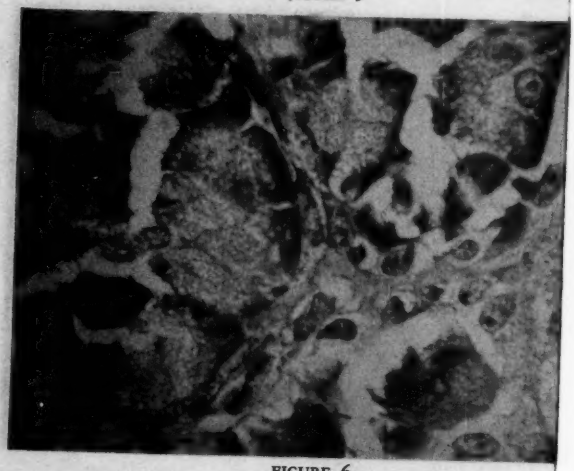

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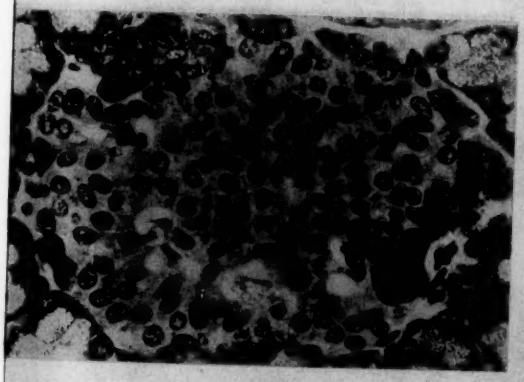

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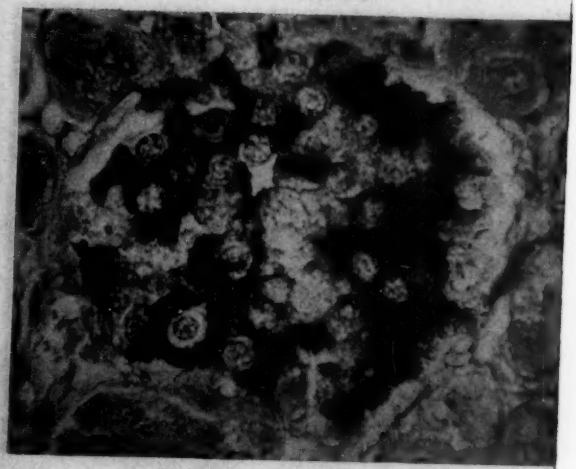

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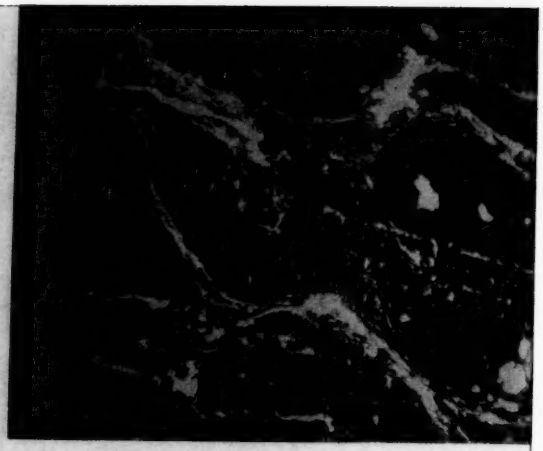

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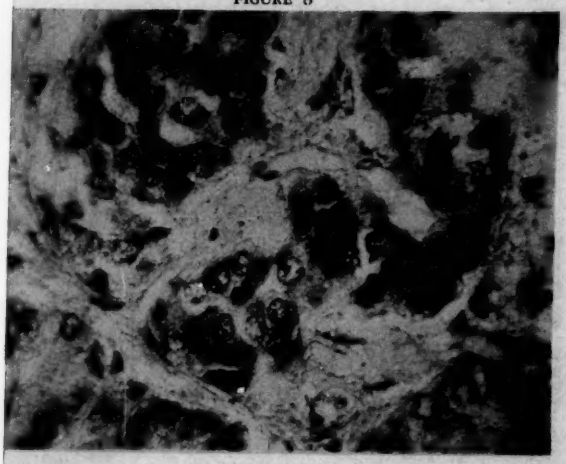

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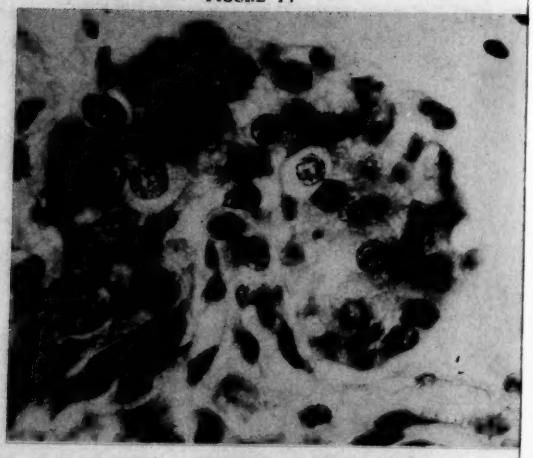

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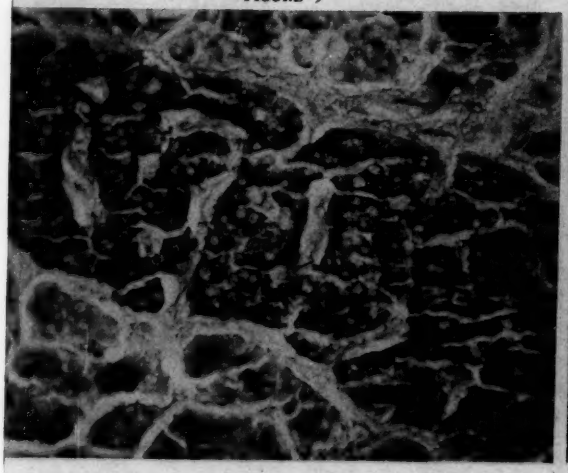

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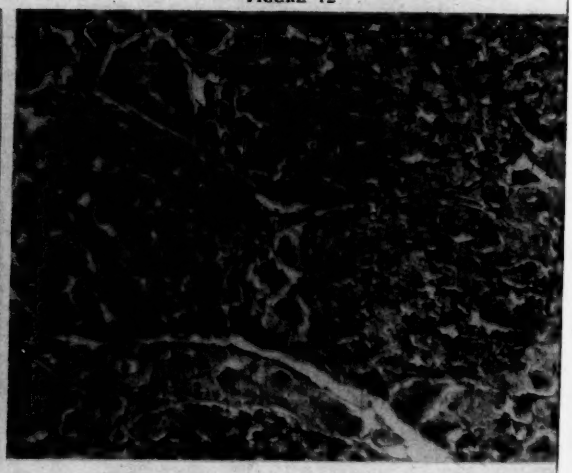

FIGURE 13

FIGURE 8 An atrophic islet from the pancreas of Leonard Thompson, the first diabetic to receive insulin. Very few granules are present in the scanty rims of cytoplasm which surround the nuclei of the islet cells. Stain and magnification as for Figure 7, with which this photomicrograph should be compared.

FIGURE 9 Pancreatic islet from the case of Dr. J. Gilchrist. Beta cells containing granules (blue) are present, but the ratio of alpha cells (red) to beta cells is higher than normal. There is hyalinization of the sinusoids throughout. Gomori's chromium haematoxylin and phloxine stain. ×1000.

FIGURE 10 A group of islet cells from the pancreas of the case reported by Wilder, Allan, Power and Robertson (see text). Many granules (purple) are present in the beta cells. Wilson's modification of Gomori's aldehyde-fuchsin stain. ×700.

FIGURE 11 Masses of islet tissue are present in this section prepared from the pancreas of the case reported by Howland, Campbell, Maltby and Robinson (see text). Haematoxylin and eosin stain. ×100.

FIGURE 12 Afferent and efferent vessels to this small islet are included in the same section. Pancreas of a case of hypoglycemia in an infant autopsied by Dr. W. L. Donohue. Gomori's chromium haematoxylin and phloxine stain. ×1000.

FIGURE 13 There is a striking increase in the number and size of the islets of Langerhans in this section of the pancreas from the case of "dysendocrinism" reported by Dr. W. L. Donohue. Wilson's modification of Gomori's aldehyde-fuchsin stain.

which we hope to be able to make from these studies is: "How much insulin in relation to the normal amount was this subject's pancreas providing for the tissues of the body?" The level of blood insulin will give us an important part of the answer we seek, but this has yet to be placed on a quantitative basis. Mr. J. M. Salter, in our department, is just beginning to achieve satisfactory assays using the Gelhorn-Bornstein technic with some slight modifications and improvements. He has successfully alloxanized his hypophysectomized rats. I have been talking about blood insulin for a long time and I congratulate Dr. Gelhorn, Dr. Anderson, Dr. Bornstein, Dr. Groen and the others who have made the present methods available. Bornstein and Lawrence[10] have already provided us with some information on the level of blood insulin which can be maintained by the "maturity onset" diabetics who have, as I have mentioned,[9] about half the normal pancreatic insulin. This average figure may well prove to have little clinical significance since each case will have to be considered as an individual. Some cases with high blood insulin may prove to require more exogenous insulin than others with a lower blood level. As I have discussed elsewhere[11] we must also learn to assay the insulin antagonists in blood. Dr. Donald Clarke, in our department, has been attempting to concentrate plasma insulin using a Kirkwood electrophoretic cell. He has secured as high as a sixfold increase in potency per unit volume with added insulin and his recent figures indicate that a similar procedure may produce a several-fold concentration of natural insulin. Perhaps he will be able to use normal or diabetic mice, more readily available test objects than can now be used to estimate the insulin content of blood.

I would now like to call attention to some other interesting pictures of islet cells. In the normal guinea pig's pancreas stained by Gomori's haematoxylin-phloxine procedure and shown in Figure 4, there is no difficulty in distinguishing alpha and beta cells. Similarly in the normal rat pancreas the peripheral alpha cells stand out clearly from the centrally located beta type. As originally shown by D'Arnozan and Vaillard (1884)[12] and by Schulze (1900),[13] ligation of the pancreatic ducts isolates the islets with waves of fibrous tissue (Figure 5). It was from degenerated pancreas like this that Banting and I extracted our first insulin in 1921. The historical importance of this fact is not decreased by the knowledge that the exact procedures which we used for the degenerated gland would have given us more insulin from the intact dog or ox pancreas.

Professor Lyman Duff, whom we are proud to claim as a Toronto graduate in Medicine (he is now Dean of Medicine at McGill), has kindly sent me examples of what we used to call hydropic degeneration, but now know from the work of Toreson and Duff[14] to be glycogen infiltration. Similar conditions can be demonstrated in metapituitary diabetes in dogs where the glycogen is found in the degenerated islet and duct cells. Preparations illustrating this were made available to me by Professor James Campbell, whose studies on the production of permanent diabetes in dogs by injection of highly purified growth hormone are now appearing in press from our Department of Physiology. In a case of spontaneous diabetes in a dog studied by Dr. Wrenshall, glycogen infiltration of the duct cells was observed (Figure 6). Dr. Hartroft studied many sections of this pancreas before he found any islets. We have many other interesting pictures confirming the effect of alloxan on beta cells and the recent findings of our Belgian colleagues of cobalt on alpha cells, but I must not pause to show them here.

Turning now to human cases, I would like to record the fact that Leonard Thompson, the first diabetic patient treated with insulin, who died of bronchopneumonia some eleven years after January 11, 1922, the

day he received his first injection, had an atrophied pancreas in which it was difficult to find any islet tissue. The beta granules stand out beautifully in the *normal* pancreas stained by the Wilson-Gomori procedure (Figure 7). The shrunken islet lacking beta granulation, illustrated in Figure 8, is from Leonard Thompson's pancreas. (I am indebted to both Dr. Walter Campbell and to the Department of Pathology, University of Toronto, for permission to use this illustration.) I have recorded elsewhere that it fell to my lot to remove the normal pancreas from a steer, make the partially purified insulin and establish its potency in diabetic dogs before Banting and I took our first injections. We gave the rest of this material to Drs. Campbell and Fletcher for the first clinical trial. The insulin was crude but active, and certain features of its preparation, such as the concentration of ethyl alcohol for the initial extraction of that normal adult beef pancreas, which I adopted after preliminary trials and testings on diabetic dogs, have been almost universally used for the past 30 years in the large-scale production of insulin.

The next figure shows the granules in the islet cells of the first doctor to receive insulin. Banting's friend and mine—Joseph Gilchrist—lived for nearly 30 years after we gave him his first injection of insulin in our laboratory in the winter of 1922. I followed his blood sugar downward and his expired air was collected for gas analysis. He had an attack of hypoglycemia about midnight on his way home from the Physiological Laboratory that night. If a pathologist studied only a limited number of islets such as the one illustrated in Figure 9, he might conclude that this pancreas should contain appreciable amounts of insulin. But there proved to be relatively few normal islets and the insulin content of the pancreas was 0.3 units per gram instead of the normal 2.4 units. The total insulin content of the pancreas was 9.8 units instead of about 200 units. The gland weighed 35 grams in contrast to a normal weight of 80 grams. We can only guess at the output of insulin, but it was presumably a very small fraction of the normal. The figures were obtained by my colleagues Wrenshall and Hartroft from the specimen made available by Dr. A. J. Blanchard of the Sunnybrook Military Hospital in Toronto.

The first case in which an excessive secretion of insulin was established by clinical and necropsy findings was that of Wilder, Allan, Power and Robertson.[15] This patient, also a physician, had profound hypoglycemia and an exploratory operation revealed a tumor mass in the pancreas with metastases in the liver. Insulin was found in one of the liver metastases as well as in the primary tumor. Through the kindness of Dr. Russell Wilder, Dr. Frank Allan and Dr. J. W. Kernohan I am able to show you a section from this historic case, stained in our laboratory by Hartroft and Wilson (Figure 10).*

The first case of islet cell tumor to recover after surgical removal of the growth was that reported from Toronto by Howland, Campbell, Maltby and Robinson.[17] A tumor about 1.5 cm. in diameter was removed by my close friend the late Roscoe Graham, and although it was originally considered probably to be carcinomatous in nature, the pathologist Dr. W. L. Robinson, who also made many contributions during the early insulin investigations, now considers that it may be classified as benign. A section from this insulin-containing tumor is shown in Figure 11.

In the most recent collection of cases with islet cell tumors, 398 in number,[18] there were 313 benign adenomas. The carcinomas numbered 37 and the others were questionably malignant. In 12.6 per cent of cases there was more than one adenoma present.

Various tissue culture experts have attempted to grow islet cell tumor tissue in vitro and to transplant the cells, which have been "acclimatized" in serum from the potential recipient, to diabetic patients. Professor Gaillard in Leiden had a few encouraging results. Dr. Marjorie Murray at the Presbyterian Hospital in New York also secured good growth but on transference to patients there was no evidence of persistent growth of insulin-producing cells.[16]

One of the most interesting sections of islets which I have seen is that illustrated in Figure 12. This is from a case of hyperinsulinism in a child studied by Dr. W. L. Donohue of The Toronto Sick Children's Hospital. Our Mr. Wilson cut many sections before he demonstrated an afferent and an efferent capillary in the same picture. One can almost see all the 16 amino acids hurrying in to keep their precise appointments with the many coupling enzymes in the busy beta cells and the purposeful outward march of the complete molecules of insulin within the efferent vessel.

Another interesting pancreas, also obtained through the kindness of Dr. Donohue, shows a large part of the field taken up with islets—there is obviously a tremendous increase in islet tissue. This child died before Dr. Lawrence Chute could conduct metabolic studies[19] but one would imagine that genetic or hormonal factors,

*Dr. Allen O. Whipple's recent review "Islet Cell Tumours of the Pancreas"[16] gives an excellent account of the historical and present aspects of this field. Dr. Russell Wilder's paper "Hypoglycemia,"[16-A] should also be consulted.

or both, operated to produce this fascinating picture, Figure 13. No histological evidence of either pituitary or adrenal overactivity was found so I must refrain even from speculating about hormonal imbalances.

Dr. Haist and I made a series of studies on the effects of diet on the insulin content of pancreas.[20] Fasting or feeding diets rich in fat greatly reduce the amount of insulin extractable. Insulin administration lowered the insulin content but removal of the pituitary or adrenals had no effect. In metadiabetes of all types, i.e., permanent pancreatic diabetes produced by chemical or hormonal agents, the insulin in the pancreas is greatly reduced or completely absent.

Since insulin is a product of the islets of Langerhans, and we believe that most cases of diabetes are characterized by either an absolute or a relative insulin deficiency, it is important to learn more about the factors which control the total amount of islet tissue. This problem has been approached by measuring the volume or weight of the islets of Langerhans under a variety of experimental conditions. The weights have been estimated, in work directed by Haist, by a special technic employing intravenous injection of neutral red, fresh tissue preparations, and the planimetric method of measurement. Both dietary and hormonal factors influence islet growth. If the intake of a balanced diet is so reduced that the individual fails to gain weight the islets fail to grow.[21] Tejning (1947)[22] found that in rats fed ad libitum there was a greater islet weight when the diet was high in carbohydrate than when the diet was rich in fat. Other evidence for a stimulating effect of carbohydrate is to be found in the increase in islet tissue which results from the continuous infusion of glucose (Woerner,[23] Haist and colleagues[21]).

The hormonal factors influencing the islets are also numerous. Insulin, itself, when given in very large amounts, depresses the growth of the islets.[24] The hormones which are apparently antagonistic to insulin tend to stimulate islet growth.

In most instances where a trophic effect of the pituitary on a gland has been established, removal of the pituitary leads to its atrophy. Hypophysectomy prevents the islets from growing normally and thus may lead to some reduction in islet weight as compared with paired-fed control animals, but this difference is small when considered in relation to the decrease in size of adrenals or gonads after pituitary removal. Hypophysectomy results in an atrophy of the acinar tissue of pancreas[25, 26] and thus increases the ratio of islet to acinar tissue in the hypophysectomized rats, even though the islet tissue itself has not increased in amount. As Haist[21] points out, this illustrates one reason for not accepting a change in islet to acinar ratio as an adequate *sole* criterion for a change in islet volume.

In intact rats, the islets can be made to grow by the injection of crude saline extracts of the pituitary gland (Richardson and Young,[27] Haist and colleagues,[21] and in hypophysectomized rats also the injection of crude saline extracts or of purified growth hormone preparations, leads to an increase in islet tissue.[28]

The thyroid gland also influences the islets and probably the pituitary thyrotropic material would do likewise. The administration of desiccated thyroid for 40 days or longer caused an increase in the weight of islet tissues as well as an increase in pancreas weight.[21] In one small series of hypophysectomized animals, thyroid administration was found by Haist and his colleagues to cause both islets and pancreas to increase in weight.[28]

A considerable amount of work on the influence of the gonads on carbohydrate metabolism and the islets of Langerhans has been carried out by Ingle[29] and by Houssay and his group. Cardeza[30] reported an increase in islet to acinar ratios in the pancreatic remnants in rats with 95 per cent of pancreas removed following the administration of estrogens. Dr. Haist's group found that injection of large doses of diethyl stilbestrol into female rats led to an increase in islet weight and in the ratio of islet weight to unit of body weight which was statistically significant, as was the increase in islet to pancreas ratio. Under the conditions of the Toronto studies, progesterone in large doses also caused an increase in islet weight. Removal of the gonads had no significant effect on islet growth. A valuable review of the effects of sex hormones on experimental diabetes has recently been published by Houssay.[31]

It was well established, of course, by the brilliant work of Herbert Evans and his colleagues, that the anterior pituitary provides a factor vital to the growth of the animal as a whole. Since the islet volume is so well correlated with body weight, it may be that islet growth is related to the growth of the animal as a whole and to the effect which body growth has on insulin requirements. Procedures which prevent body growth, such as restriction of caloric intake, also interfere with islet growth. The manner in which the demand for insulin is transmitted from the cells of the body to those of the islets is not known. It is possible that, directly or indirectly, an increase in blood sugar level or a change in blood insulin may set in motion physiological events which affect islet activity. This is yet another set of obviously related physiological facts for which the mechanism of interrelation remains obscure. Insulin may

be the most essential anabolic hormone, and processes relating to fat, glycogen or protein formation may call for an increased supply. However, we have far to advance before we can read all these signals.

ON THE CHEMISTRY OF INSULIN

For many of us, insulin is the most interesting of all proteins. It obviously has a charm also for the protein chemists, for they know more about its structure than about that of any other protein.

The protein chemist says that he is devoted to insulin not because of its physiological significance and therapeutic value, but because its peptide chains are relatively short! It is stable in acid and reversibly inactivated in mild alkali. It can be readily crystallized. It is practically the only protein which can be purchased in large amounts in a pure form. In spite of this array of facts, I still feel that the chemist's interest is subconsciously catalysed by the realization that in the completely diabetic organism one molecule of insulin accounts for the utilization of some 15,000,000 molecules of glucose per hour[32] and that the lives of many people are prolonged by its daily use.

It was first isolated in crystalline form by Abel in 1926.[33] In 1934, David A. Scott* showed that it could be readily crystallized as the zinc salt and that Abel's crystals contained zinc. Nickel, calcium and cobalt also aid in effecting crystallization of insulin preparations.[34, 35] There is about 0.5 per cent of metal in the crystals. The "salts" of the insulin protein may appear in various forms—the zinc compound usually as twin plate-like rhombohedra. Chemical analysis by Brand[36] and by the Cambridge workers under the leadership of A. C. Chibnall[37, 38, 39] indicate that the insulin molecule is built up entirely or almost entirely of amino acids. Insulin is richer in the amino acids leucine, glutamic acid, and cystine than most other proteins; methionine, tryptophane and hydroxyproline, which are common in many proteins, are absent from the insulin molecule.

The maximum molecular weight of insulin is 48,000; *p*H 7.0—7.5; protein concentration 0.4—0.9 per cent. However, when more dilute solutions of the hormone are used below *p*H 4 or above 7.5 the insulin molecule dissociates into subunits having a molecular weight of about 12,000 (Gutfreund[40]). This is probably the physiological form of insulin although the physical chemists are actively debating the possibility of a smaller unit.

When insulin is oxidized with performic acid the molecule is split into its separate polypeptide chains. Two fractions can be isolated: A, an acidic fraction containing no basic amino acids and B, a basic fraction. These two physiologically *inactive* components are normally linked together by the -S-S- bridges of cystine and perhaps by other as yet unknown bonds. This work of Sanger's[41] led to the conclusion that the 12,000 molecular weight insulin is composed of two identical A chains and two identical B chains. Sanger made a great contribution by introducing the use of partial hydrolysis of dinitrophenyl derivatives of the fractions to determine the sequence of the amino acid components. He had available the invaluable tool of paper chromatography of Martin and Synge[42] and the newer knowledge of the chemical linkages attached by specific enzyme systems, such as pepsin, trypsin and chemotrypsin. The exact sequence of all the amino acids in the two chains of insulin is now known but we are still far removed from the knowledge of how the chains are formed and joined together in the beta cells of the islets.

When a dilute acidic solution of insulin containing a small amount of salt is heated, a flocculant precipitate forms.[43] In experiments in which slightly different conditions were used, Waugh[44] has shown that the insulin can be modified to yield fibrils. The rate of fibril formation increases with increasing hydrogen ion, salt and protein concentration, and with temperature. In fibril formation two reactions are involved. First the formation of active centres, and second the elongation of these into fibrils. These fibrils have little or no antidiabetic activity but can be converted into active insulin, as can the so-called heat precipitate of insulin, by changing the reaction to the alkaline side. Seeding an insulin solution with fibrils may bring about a complete conversion of the active insulin into inactive fibrils.

This brief and inadequate glimpse of a few of the chemical properties of insulin may stimulate those of us whose activities lead us far away from this highly specialized and fascinating field.

ON THE ACTION OF INSULIN

The dramatic fall in blood sugar, the cessation of glucose excretion, and the even more exciting recovery of our moribund diabetic dogs when insulin was given, stimulated Banting and me to ask ourselves in July 1921: "How does it act?" Banting asked me: "How can we tell what it actually does to the sugar which

*The first chemist to share the responsibility with me for the large scale production of insulin in Canada was D. A. Scott, and he was soon carrying a great part of the load. You all know his record of achievement in this and other fields, and I would like to acknowledge here his constant help over the thirty years of our friendship.

disappears from the blood?" I suggested that we should determine the oxygen consumption and carbon dioxide output before and after insulin in our depancreatized dogs. This was the first exploration of the action of insulin ever proposed. Banting was interested but as he remarked: "I know just as much about respiratory quotients as you do about intussusception." I had never heard of the latter until one of our depancreatized dogs exhibited the signs which Banting suggested and later demonstrated were caused by this condition. With the help of Dr. John Hepburn, these respiratory studies were made on diabetic dogs and on the first diabetic doctor to receive insulin. Dr. Gilchrist's respiratory quotient mounted as his blood sugar fell. I used some of these initial findings on respiratory exchange after insulin in man and dogs as part of my M.A. thesis in Physiology. It was a sketchy effort written at the last moment in a single evening, for we had at that time again completely lost the long-buried secret of how to make insulin in sufficient amounts for the treatment of diabetic patients. Some of the patients who had been "brought back" by insulin died, and our struggles to regain the necessary knowledge made even the fascinating pursuit of physiological action impossible at that time.

However, before many months had passed, the Toronto group had established a number of points about the action of insulin. Banting and I, in addition to discovering its effect on blood and urinary sugar, had secured preliminary indications of decreased nitrogen and ketone body excretion. We had, of course, repeatedly demonstrated the complete and prolonged "clinical" recovery of our depancreatized dogs when treated with an alcoholic extract of commercial beef pancreas. We noted the more normal, less yellow appearance of the livers of our treated dogs. With Prof. Macleod, Collip, Noble and Hepburn we reported the formation of liver glycogen, the abrupt cessation of ketosis, the rise in R/Q, the fall in blood and liver fat and the gain in weight and strength after insulin administration. At one time I had hoped to present a brief sketch in this lecture of the efforts of the many individuals and laboratories that have given us our present knowledge of the effects of insulin on carbohydrate, fat, protein, phosphorus and potassium metabolism. This is out of the question; but it seems to me that the picture of insulin as perhaps the central anabolic hormone is being drawn. Many of the great names in present day research on metabolic processes have contributed to and discussed this general subject which, in its broader aspects, is of course the integration of many, perhaps all, endocrine-stimulated anabolic processes. I did make a list of twenty prominent names among those interested in the mechanism of action of the pituitary growth hormone, the adrenal corticoids, the sex hormones and the thyroid hormone, and in the part which the presence of insulin may play in many of these activities. But this making of "lists" is a dangerous practice! I hope to know a lot more about these subjects before the end of July when many of those whom I listed, and others equally interested, will have devoted two weeks in London and in Leiden to discussions of carbohydrate metabolism. Prof. Frank G. Young and I have been named as Chairmen of these two Conferences.

We have become actively interested recently in the extent to which other anabolic hormones may depend on insulin for the production of their effects. I will have to refer you to the articles written by workers who have contributed much more to this subject than we have. Mirsky, Evans and Li, Young, Evans, Long, Lukens, Milman and Russell, de Bodo, Cori, Stadie, Lotspeich, De Jongh, Wilhelmi and many others have discussed aspects of this matter in recent years.

It may be that many of the previous conclusions about purified growth hormone preparations will have to be revised when the Raben-Astwood material, which has been stated not to be diabetogenic, has become available. The changes may, however, merely affect the names of the fractions responsible for the effects produced by cruder extracts. It is obvious that someone must determine (a) what constituent of pituitary exerts the insulin-reversible inhibition in Cori's cell-free hexokinase system; (b) what properties are responsible for the differences between the in vitro effects of crude pituitary extract and purified growth hormone on glycogen formation in the diaphragm in Stadie's experiments; (c) whether the same constituent lowers the blood sugar in normal rats (Milman and Russell) but fails to do this in normal dogs (de Bodo, Sirek); (d) whether the increased volume of the islet cells and perhaps their insulin output, produced by the pituitary principle or principles, are the result or the cause of the augmented appetite and food intake. In one of Dr. Sirek's studies in my laboratory, the same purified growth hormone preparation which produced no change in blood sugar in the normal dog caused a prompt and extensive rise in the same animal after complete pancreatectomy. What prevented the rise in blood sugar of the intact animal? Could it have been the liberation of insulin or do these pituitary preparations contain both a hyperglycemic and a hypoglycemic factor with the "balance of power" dependent on the state of the field of action? De Bodo only ob-

tained a fall in blood sugar after growth hormone in depancreatized dogs when the material was given soon after pancreatectomy. Sirek has now demonstrated this with one growth hormone preparation much longer after pancreatectomy. There may, of course, have been a trace of natural or exogenous insulin present under both these conditions. Krahl's work demonstrates an insulin-like effect of purified growth hormone on blood sugar and diaphragm in alloxan-diabetic rats. It is abundantly apparent that more good chemistry is needed before the physiologist and biochemist can push forward with confidence.

Under the standardized conditions of Sirek's experiments, purified growth hormone preparations do not lower the blood N.P.N. of normal dogs. Testosterone does lower the N.P.N. of normal dogs but not of pancreatized dogs without insulin. Insulin lowers the N.P.N. of depancreatized dogs and testosterone does not supplement the insulin effect.

Mr. Salter and I thought it would be interesting to study the growth effect of insulin in the absence of the pituitary gland. This has not been investigated because everyone knows how very sensitive hypophysectomized animals are to insulin. Some species die in hypoglycemia without administered insulin if fasted for even a relatively short period. Now the tests for the pituitary growth hormone utilize principally the weight increase in "plateaued" hypophysectomized rats, increase in body and tail length, increase in organ size, widening of the epiphyseal line of the tibia, and nitrogen retention. When in our initial experiment a small dose of insulin was given to an hypophysectomized rat, his appetite and food intake were increased and he began to grow. The dose was rapidly stepped up from 1 unit to 6 units of protamine zinc insulin per day. The animal put on weight, his body and tail increased in length, his organs (liver, heart and thymus) gained in weight, his epiphyseal line widened and from later determinations on other comparable animals, he undoubtedly retained a lot of nitrogen, presumably in large part as protein. These preliminary findings will, of course, be extended and published in due course (Figure 14). This work proves that insulin is a growth hormone which apparently can operate in the absence of the pituitary gland. Before insulin was given the rats did not grow. Their sex glands and adrenals continued to decrease in weight in spite of the growth effect of insulin. At autopsy their sella turcicae confirmed the absence of appreciable amounts of pituitary gland and serial sections are in process. It would appear, judged by the criterion of independent action, that in the rat, insulin is a more indispensable growth hormone than somatotropin. Perhaps one of the causes of cessation of growth after removal of the pituitary is decreased secretion of insulin. The islets do not atrophy but some essential stimulus for the liberation of insulin may be lacking. A small amount of somatotropin may have remained in our experiments, although this appears unlikely; but no one would suggest that insulin exerts its anabolic effects through increased liberation of somatotropin. The two hormones are certainly essential synergists for normal growth, but we wish to know just how much insulin is liberated in the hypophysectomized animal. To what extent could decreased insulin secretion account for the lack of growth in hypophysectomized animals? To what extent can large unphysiological doses of insulin compensate for the lack of physiological amounts of the growth hormone? My young colleague, Mr. Salter, has found that all the hypophysectomized rats die if given even very small amounts of regular insulin. A slow acting insulin and a high carbohydrate diet constantly available in an attractive form are essential. The first insulin we used may have contained a very little hyperglycemic factor. The last series of rats were given insulin free of this material and the results are similar. This work opens up a new vista to us. We must study the effect of insulin on growth, nitrogen retention, etc. in the hypophysectomized depancreatized preparations. We must know the extent of the participation of each of the other hormones in the growth effect of insulin and we must compare the results of forced feeding and of pituitary growth hormone administration with those of insulin under exactly comparable conditions in normal, depancreatized, hypophysectomized and Houssay animals. Several of these studies are in progress.

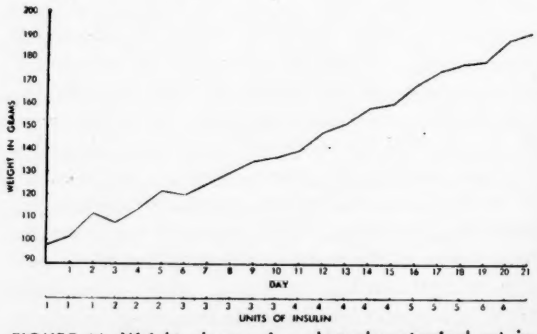

FIGURE 14 Weight changes in a hypophysectomized rat induced by daily administration of protamine zinc insulin. This animal showed no weight change during a five-month period prior to insulin treatment. Throughout its life it was fed ad libitum on a complete diet.

Thus the thirty years since Banting and I discussed how insulin acts have not witnessed the solution of all the problems. The current literature is full of valuable articles on this subject. Not long before his death Banting and I discussed working again together in the laboratory. We had selected a problem in carbohydrate metabolism and had planned a combined surgical and chemical approach.

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The Inheritance of Diabetes Mellitus

AN ANALYSIS OF THE FAMILY HISTORIES OF 1,631 DIABETICS

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The role of heredity as an important factor in the etiology of diabetes mellitus is conceded, chiefly on the basis of multiple examples of the disease in family groups and its coincidental occurrence in uniovular twins. The precise mode of transmission of the disorder, however, is by no means clearly understood; not any of the hypotheses that have been advanced to explain the hereditability of diabetes have received general acceptance.

The genetic aspect of diabetes is complicated by an absence of complete concordance between the diabetic genotype and the diabetic phenotype, owing to the variabilities of onset age and the severity of the disease as observed clinically. Diabetes mellitus may occur at any age, but frequently it does not become manifest until middle life or later, and the intensity of the disturbances of the metabolic processes may vary in degree from subclinical to severe, even to the extreme of being lethal. Since many persons exist, presumably, who have a mild diabetes of which they are ignorant and since numerous potential diabetics doubtless die of unrelated maladies prior to the actual manifestation of the diabetes, theoretical genetic ratios are incapable of fulfilment. On the other hand, a propitious characteristic pertaining to the diabetic state, from the standpoint of genetic study, is its identification and assessment in terms of certain determinate biochemical criteria.

Since the subject of heredity in diabetes has been reviewed recently by others[1, 5, 8, 9, 11] only the main trends in the development of the present knowledge are discussed. The published pedigrees of diabetics exhibit a wide variety of patterns of inheritance. Because of the well-known fact that individual family histories may be misleading, possibly the chief inference to emerge from an examination of such pedigrees is that the results of population surveys or Diabetes Detection Drives may prove to be more profitable than the usual pedigree studies in clarifying the problem of the genetics of diabetes. Since diabetes is a relatively common disease, individual pedigrees are less revealing than they often are in the case of a comparatively rare disorder.

Probably the first large series of diabetic patients investigated from the standpoint of heredity was that reported by Cammidge,[3, 4] who found a positive family history of diabetes in 396 of 1,000 cases. Of these, he regarded 197 as being "recessive" and 199 as "dominant"

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and he emphasized the relatively higher proportion of "recessive" histories among the younger patients.

Pincus and White,[13] in presenting data based upon 523 case records, found the incidence of diabetes to be increased in the families of diabetic patients, as compared with the families of a group of nondiabetic individuals. They also observed that the proportions of affected sibs when neither, one, or both parents were diabetic agreed reasonably well with the proportions expected on the basis of recessive inheritance, when appropriate corrections for the variability of onset age were applied. Although these conclusions have not been universally accepted, the hypothesis of the recessive inheritance of diabetes appears to be well founded.

A different hypothesis has been proposed by Levit and Pessikova,[10] who studied the family histories of 252 diabetics. The rather widely publicized idea that diabetes is inherited as a dominant with reduced "penetrance," first advanced by these writers, is based solely upon their observations. Since they do not appear to have taken into account the variability of onset age of the disease, certain of their interpretations of the data are open to question. Their conclusions, therefore, should not pass unchallenged.

Neel,[11] whose particular interest in the subject rests in the possibility of the detection of genetic carriers, points out that in addition to an increased incidence of clinical diabetes amongst the relatives of diabetic patients as compared with nondiabetics, an impressively high prevalence of abnormal glucose tolerance curves, indicative of impaired carbohydrate metabolism, has been observed in the apparently normal relatives of diabetics. He suggests that such potentially diabetic individuals may transmit a similar tendency to their descendants.

The view that diabetes may be inherited as a recessive *or* as a dominant has had the support of several investigators, including Cammidge,[3, 4] Wright,[18] and recently Harris,[6, 8] who noted an increased rate of parental consanguinity for "juvenile" as compared with "adult" diabetics. Harris considered "juvenile" diabetics to be homozygous and "adult" diabetics heterozygous for the diabetic gene.

The possible genetic basis for a correlation between the onset age and the degree of severity of the diabetes has claimed attention. That these features of the disease are in some way associated is indicated by the general clinical experience that the pertinent metabolic derangement is inherently more acute and more severe in the juvenile cases than in the senile cases. Twin studies[2, 9] have shown that the onset age and the degree of severity tend to be closely parallel in uniovular but less so in binovular twin pairs, suggestive of a true genetic influence. Penrose and Watson[12] discussed the possibility that the secondary factors affecting the age at onset and the severity might be sex-linked. Harris[8] investigated in detail the onset age relationships among diabetic sibs and diabetic parent-offspring pairs and concluded that the onset age was positively correlated in sibs but noncorrelated, or very slightly so, in parents and offspring.

Steinberg and Wilder[15] have shown that "anticipation," or the alleged tendency for diabetes to appear at earlier ages in successive generations, is the result of statistical rather than biological phenomena and that no association appertains to the ages of onset in parent and child. A tendency for diabetes to affect chiefly males in some pedigrees and chiefly females in others has been suggested by Penrose and Watson[12] and Harris.[7]

THE PRESENT INVESTIGATION

The availability of a considerable number of detailed family histories of diabetics, derived mainly from the essentially stable population of Western Ontario, has provided an opportunity for a protracted genetic study of diabetes. A systematic register of all the diabetic patients observed at the Victoria Hospital, London, Ontario, has been in effect since 1929. The series was reviewed by Penrose and Watson in 1945 and the present survey was undertaken as a follow-up of their project after a five-year interval. The data which accrued during the years 1945 to 1950 and which comprise the basis of this report involve the material of the previous review only to the extent of including pedigrees to which newly discovered familial cases of diabetes had been added.

For the purpose of the present investigation, the familial data pertaining to 1,631 diabetics were obtained by means of inpatient and outpatient hospital records, correspondence and personal interviews. In each instance, detailed information was sought concerning the parents, sibs and offspring of the propositi. Their present age or age at death, the presence or absence of diabetes mellitus and, if this existed, the age at the time of its onset were recorded. Knowledge of the existence of diabetes in more distant relatives was also elicited and, if present, the age at onset and the precise relationship to the propositus was ascertained, if possible. Inquiry was made regarding the occurrence of diabetes in the spouse and in the relatives of the spouse; also of the existence of consanguinity in the parents. The desired details could not always be obtained accurately and completely, but for each of the following analyses only those histories in which the relevant information was complete and de-

pendable have been included. However, under no circumstance was the number of histories excluded sufficient to introduce a factor of bias into the findings.

The age distribution of the propositi at the time of the onset of the diabetes and at the time of the investigation, according to sex, is given in Table 1. Since it was frequently impossible to specify with any degree of certainty the age at which the diabetes first developed, the "age at onset," as used here, refers to the age at which the disease was first definitely recognized. Table 1 shows a typical distribution for diabetes mellitus. The series included 951 females (58.3 per cent) and 680 males (41.7 per cent). The mode of the onset age falls in the first half of the sixth decade for both sexes, the numbers of males and females being roughly similar up to the age of approximately 40 years, after which the number of female diabetics rises much more rapidly than the number of males.

The findings for the sibs, parents and offspring of the propositi are presented and discussed separately.

The Sibs

THE INCIDENCE OF DIABETES IN THE SIBS. There were 4,631 sibs of the diabetic propositi for whom the data regarding the sibships were credible. Only those sibs who survived to the age of one year were included, since frequently the knowledge pertaining to those who had died during the first year of life was lacking entirely or was equivocal. Diabetes existed in 415 sibs (8.96 per cent). This figure is somewhat greater than the findings of other writers, e.g. Pincus and White, 5.53 per cent; Levit and Pessikova, 4.59 per cent; Harris 4.34 per cent.

Table 2 shows separately the numbers of diabetic sibs of propositi with neither, one, or both parents affected with diabetes mellitus. This table is based upon data for 828 propositi with neither parent affected, 166 with one parent affected, and four with both parents affected. Propositi without sibs or for whom the data concerning the sibs were incomplete have been excluded from this analysis. Necessarily, Table 2 portrays only an approximation of the desired computation of the proportion of affected sibs according to the parental genotypes. Since it was impossible to determine the genotype of the parent or of any sib unless he or she had already developed diabetes, a classification according to the phenotype seemed to be the logical alternative.

When neither parent was diabetic, 7.69 percent of the sibs were likewise affected and, when one parent was diabetic, 15.30 per cent of the sibs were diabetic. These percentages are in the ratio of 1:1.99 and thus approximate closely the 1:2 ratio expected on the basis of the recessive inheritance of a single autosomal gene. The findings for the few instances in which both parents were diabetic fail to contribute additional evidence. Of 24 sibs in the four sibships in this category, only two (8.33 per cent) were affected. This percentage is, admittedly, lower than expected, but a rational interpretation can not be founded upon so small a sample. In general, however, these data suggest but do not prove the recessive inheritance of diabetes mellitus.

The relative proportions of sibs affected according to the parental phenotypes, as reported by other authors, are variable, as the following tabulation indicates:

Authors	Percentage of Sibs Affected		
	Neither parent affected	One parent affected	Ratio
Steinberg and Wilder[14]	6 (approx.)	12 (approx.)	1:2
Pincus and White[13]	4.23	10.70	1:2.5
Harris[8]	3.48	11.70	1:3.36

Table 3 presents the data contained in Table 2, rearranged to show the incidence of diabetes in the sibs according to the onset age of the propositi. No statistically significant difference derives from the percentages ($x^2 = 2.885$; D.F. $= 4$; $0.50 < P < 0.70$). In other words, diabetes appeared with approximately equal frequency in the sibs, regardless of the onset age of the propositi. It might be deduced, therefore, that the sibs who are genetically predisposed to diabetes tend to develop the disease at approximately the same age as the propositi. However, such a deduction is not valid because no information is yet at hand regarding the proportion of the sibs of the early-onset propositi who may be predestined to develop diabetes later in life. The proportion probably will rise significantly, since the early-onset propositi and their sibs at the time of the survey comprised a comparatively youthful group of individuals.

THE SEX DISTRIBUTION OF SIB PAIRS. Since diabetes has been claimed to affect chiefly males in some kinships and chiefly females in others,[7, 12] the data for 487 pairs were classified to test this contention. The observations are summarized in Table 4. The fact that diabetes mellitus affects males and females unequally, with a sex ratio that varies with age, must be given consideration in determining the expected values. The sex ratio for the propositi was 0.40:0.60 and for the sibs 0.43:0.57. The expected proportions of sib pairs were calculated on this basis as follows:

TABLE I Age at Onset and at Investigation of 1,631 Diabetic Propositi

Age at Onset (Years)	Age at Investigation (Years) 0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	Total
								Males											
0-4	1	4	2	3	1														11
5-9		2	3	6	3	1	1												16
10-14			5	3	6	3	2	1											20
15-19				4	3	5	3	3	2	1									21
20-24					4	3	3	2	1	2									15
25-29						6	6	8	3	2	2								27
30-34							9	7	6	3	4	1							30
35-39								11	11	10	6	5	1						44
40-44									17	9	6	5	4	2					43
45-49										31	15	15	4	10	4	1	1		81
50-54											30	28	16	5	6	—	—		85
55-59												36	23	14	6	3	1		83
60-64													35	19	11	6	1		72
65-69														28	25	5	1		59
70-74															26	11	—		37
75-79																23	2	1	26
80-84																	6	2	8
85-89																		2	2
	1	6	10	16	17	18	24	32	40	58	63	90	83	78	78	49	12	5	680
									Females										
0-4	1	2	1	1	—	1													6
5-9		3	4	6	5	3	1												22
10-14			2	2	3	6	1	1	1										16
15-19				2	6	7	4	4	1										24
20-24					6	6	4	3	—	3									22
25-29						9	8	4	2	2	3								28
30-34							8	6	7	5	6	1	—	1					34
35-39								10	9	8	12	7	3	2					51
40-44									14	18	16	13	4	2	1				68
45-49										18	29	27	12	8	2				96
50-54											42	40	34	18	10	3			147
55-59												48	40	32	14	3	1		138
60-64													45	39	14	3	6		107
65-69														48	34	12	1		95
70-74															23	26	4	1	54
75-79																23	1	2	26
80-84																	12	3	15
85-89																		2	2
	1	5	7	11	20	32	26	28	34	54	108	136	138	150	98	70	25	8	951

Propositus	Sib	Proportion Expected	Number Expected
M	M	0.40 x 0.43	83.76
M	F	0.40 x 0.57	111.04
F	M	0.60 x 0.43	125.65
F	F	0.60 x 0.57	166.55
Total			487.00

The existence of an excess of like-sexed pairs could then be readily tested. As Table 4 indicates, the excess of like-sexed pairs is insignificant and it may be concluded that for the present series, at least, the apparent tendency for diabetes to occur with greater frequency in the like-sexed than in the unlike-sexed sibs of the propositi is a statistical phenomenon, fully explainable on the basis of the relative numbers of males and females affected. Therefore, no genetic relationship exists between the sex of the propositus and the sex of the affected sibs, insofar as the diabetes is concerned.

The Parents

THE INCIDENCE OF DIABETES IN THE PARENTS. Of the 3,262 parents of the diabetic propositi, diabetes was known to be present in 231 (7.08 per cent). Only 174 of these diabetic parents appear in Table 2, the remaining 57 being either the parents of "only" children or the parents of diabetics regarding whose sibs the data are incomplete. The findings of other workers are in reasonably close agreement with our observations, e.g. Pincus and White, 8.33 per cent; Levitt and Pessikova, 4.34 per cent; Harris, 5.03 per cent.

CONSANGUINITY. If a trait is inherited through a recessive autosomal gene and if the trait be rare, there is a concentration of affected individuals among the offspring of consanguineous unions. Harris[6] detected an increase in the incidence of parental consanguinity among diabetics

TABLE 2 Incidence of diabetes in the sibs of the propositi, classified by the phenotypes of the parents

Age of Propositus at Onset (years)	Neither Parent Affected		One Parent Affected		Both Parents Affected		Total	
	No. of sibs	No. affected	No. of sibs	No. affected	No. of sibs	No. affected	No. of sibs	No. affected
0-4	15	1	1	—	—	—	16	1
5-9	73	6	3	—	—	—	76	6
10-14	95	5	—	—	—	—	95	5
15-19	50	1	5	3	—	—	55	4
20-24	119	10	11	3	—	—	130	13
25-29	73	4	37	3	6	—	116	7
30-34	119	7	61	12	—	—	180	19
35-39	152	9	73	15	7	1	232	25
40-44	217	8	42	5	—	—	259	13
45-49	330	38	119	12	5	—	454	50
50-54	601	51	120	17	6	1	727	69
55-59	658	51	100	15	—	—	758	66
60-64	457	45	90	17	—	—	547	62
65-69	441	32	66	13	—	—	507	45
70-74	215	14	43	3	—	—	258	17
75-79	143	9	—	—	—	—	143	9
80-84	76	4	—	—	—	—	76	4
85-89	2	—	—	—	—	—	2	—
	3836	295	771	118	24	2	4631	415

TABLE 3 Incidence of diabetes in the sibs of the propositi. grouped data from table 2

Age of Propositus at Onset (Years)	Total No. of Sibs	No. of Diabetic Sibs	Percentage Diabetic
0-14	187	12	6.42
15-29	301	24	7.97
30-44	671	57	8.49
45-59	1939	185	9.54
60+	1533	137	8.94
	4631	415	8.96

TABLE 4 The sex distribution of 487 diabetic sib pairs

Propositi	Sibs		Total
	Male	Female	
Male	95	102	197
Female	115	175	290
	210	277	487

Type of pair	No. observed	No. expected*
Like-sexed	270	250.31
Unlike-sexed	217	236.69
	487	487.00

$X^2 = 3.19$; D.F. $= 1$; $.05 < P < .10$

*See text for method of calculation of expected values.

in whom the disease developed in early life. He proposed the existence of genetic differences between the early-onset and late-onset forms of diabetes, whereby one or more recessive genes determine at least some, perhaps all, of the early-onset cases.

Consanguinity in the parents of the propositi was encountered in nine instances in the present study (0.55 per cent). These examples are listed in Table 5. Unfortunately, no data were available regarding the incidence of cousin marriages in the general population from which the diabetic series was derived. The percentage of patients with a history of consanguineous parentage was 0.88 for those with onset before the age of 30 years and 0.43 for those with onset after the age of 30. Obviously, no conclusions can emanate from findings based upon such a small group of instances.

THE SEX OF PARENT-OFFSPRING PAIRS. Penrose and Watson[12] reported that father-son and mother-daughter pairs of diabetics occurred more frequently than father-daughter and mother-son pairs. The data of the present series were tested to determine whether or not such an excess of like-sexed pairs obtained. The findings are given in Table 6.

The expected numbers have been calculated in the manner previously described for sib pairs. Here the sex ratio among the propositi was 0.45:0.55 and among the parents, 0.32:0.68. The observed values did not differ from the expected. Therefore it would seem that the tendency for diabetes to appear slightly more frequently in the like-sexed than in the unlike-sexed parents of diabetic propositi is a statistical phenomenon explicable on the basis of the relative numbers of males and females affected and that no genetic correlation obtains between the sex of the propositus and the sex of the affected parent with respect to the diabetes.

TABLE 5 Consanguinity in the parents of diabetic propositi

Sex	Propositus Onset Age	Type of Family History	Relationship of Parents
F	23	Negative	First cousins (father's father and mother's mother were brother and sister).
M	25	Positive	"Second cousins" (precise relationship not known).
F	36	Bilateral Positive	Second cousins once removed (father's father's father and mother's mother's father's father were brothers).
M	53	Negative	First cousins (father's father and mother's father were brothers).
M	54	Negative	First cousins (father's mother and mother's father were brother and sister).
F	57	Negative	Second cousins (father's mother's father and mother's mother's father were brothers).
F	63	Negative	First cousins (father's mother and mother's mother were sisters).
F	70	Negative	"Second or third cousins" (precise relationship not known).
M	76	Negative	First cousins (father's mother and mother's mother were sisters).

The Offspring

THE INCIDENCE OF DIABETES IN THE OFFSPRING. There were 2,747 offspring of the diabetic propositi and of these 59 were known to be diabetic, giving an incidence of 2.15 per cent. This percentage undoubtedly will increase with the passage of time and the increase of the average age of the individuals concerned.

The prediction regarding the probability of the development of diabetes in the offspring when a spouse is diabetic or possesses a diabetic family history is a matter of considerable practical importance. In Table 7 the total number of offspring and the number of diabetic offspring of the propositi are given separately for those cases in which (a) the spouse of the propositus was nondiabetic and had a negative family history, (b) those in which the spouse was nondiabetic but presented a positve family history, and (c) those in which the spouse was diabetic. It is to be noted that the incidence of diabetes in the offspring was higher when the spouse of the propositus was diabetic or a member of a diabetic family than otherwise. For these two groups of offspring

TABLE 6 The Sex Distribution of 231 Diabetic Parent-Offspring Pairs

Propositi	Parents: Male	Parents: Female	Total
Male	39	65	104
Female	36	91	127
Total	75	156	231

Type of pair	No. observed	No. expected*
Like-sexed	130	121.10
Unlike-sexed	101	109.90
Total	231	231.00

$X^2 = 1.375$; D.F. $= 1$; $.50 < P < .70$

*See text for method of calculation of expected values.

TABLE 7 The incidence of diabetes in the offspring of the propositi, classified by the phenotype and type of family history of the spouse

Age of Propositus at Onset (years)	Spouse Nondiabetic with Negative Family History: No. of offspring	Spouse Nondiabetic with Negative Family History: No. diabetic	Spouse Nondiabetic with Positive Family History: No. of offspring	Spouse Nondiabetic with Positive Family History: No. diabetic	Spouse Diabetic: No. of offspring	Spouse Diabetic: No. diabetic	Total No. Offspring	No. Diabetic Offspring
0-14	5	—	—	—	—	—	5	—
15-29	96	1	3	—	—	—	99	1
30-44	366	7	10	1	2	—	378	8
45-49	1128	18	82	4	55	—	1265	22
60+	935	22	23	3	42	3	1000	28
	2530	48	118	8	99	3	2747	59

(each with a bilateral positive family history), the overall incidence of diabetes was 5.07 per cent, or more than double that for the group possessing a one-sided positive family history (1.90 per cent). Although the total number of diabetic offspring observed is small, the trend is obvious.

As shown previously, the age at onset of diabetes is in general earlier in those cases with a bilateral positive family history than in those which have a unilateral positive or a negative family history.[16, 17] Thus it is possible that the higher percentage of affected offspring in the group with bilateral family histories of diabetes merely reflects an earlier mean onset age.

Table 8 gives grouped data from Table 7 to show the percentage of affected offspring according to the onset age of the propositi. The incidence of diabetes was insignificantly different in the various age groups. However, the relatively small numbers of affected offspring belonging to the early-onset propositi do not permit a rational appraisement.

TABLE 8 The Incidence of Diabetes in the Offspring According to the Age at Onset of the Propositi. Data from Table 7

Age at Onset of Propositus (years)	No. of Offspring		No. of Offspring Diabetic		Percentage of Offspring Diabetic	
0-14	5		—		—	
15-29	99	482	1	9	1.01	1.87
30-44	378		8		2.12	
45-59	1265		22		1.74	
60+	1000		28		2.80	
	2747		59		2.15	

DISCUSSION

Although a definitive scheme of inheritance of diabetes mellitus can not be established on the basis of the data presented, the observation that the proportion of affected sibs when one parent was diabetic was approximately twice as great as when neither parent was so affected is suggestive of inheritance by a single autosomal recessive gene.

An examination of the relative numbers of like-sexed and unlike-sexed sib pairs and parent-offspring pairs leads to the assumption that, for the present series, the apparent tendency for diabetes to favor mainly males in some pedigrees and mainly females in others is a statistical phenomenon arising from the fact that diabetes does not affect the sexes equally and that diabetes is as prone to affect the unlike-sexed as the like-sexed relatives of the propositi.

The incidence of diabetes in the offspring of affected persons is higher when the spouse is diabetic or of a diabetic family (i.e. when the offspring have a bilateral diabetic family history) than when the spouse is non-diabetic and a member of a family in which the existence of diabetes is unknown (i.e. when the offspring have a unilateral diabetic family history). The current knowledge has not determined definitely whether those with a bilateral diabetic family history actually inherit a greater susceptibility to the development of diabetes or whether the higher incidence represents an earlier mean onset age in the particular group. Perhaps both factors may be operative.

The observed incidence of diabetes among the progeny of two diabetics was 8.33 per cent in the sibs of propositi with both parents affected and 3.03 per cent in the somewhat younger group who were the offspring of propositi married to diabetics. These percentages are unexpectedly low even when the variability of the onset age is taken into account, particularly in view of the finding of Harris[8] that onset age is positively correlated in sibs. It is true that our figures are derived from comparatively small series of cases; nevertheless, they are in general accord with the observations of other writers that the incidence of diabetes in the offspring of two diabetics is decidedly less than the 100 per cent expected if the inheritance of diabetes be as a single autosomal recessive. Much remains to be learned regarding the various factors, both genetic and extra-genetic, which determine the age and degree of manifestation of diabetes in genetically predisposed individuals.

SUMMARY

Diabetes was present in 415 (8.96 per cent) of 4,631 sibs of diabetic patients.

When neither parent was diabetic, 7.69 per cent of the sibs were diabetic and when one parent was diabetic, 15.30 per cent of the sibs were diabetic. These percentages give a ratio of 1:1.99 which approximates closely the 1:2 ratio expected on the basis of recessive inheritance.

Diabetes appeared with approximately equal frequency in the sibs, regardless of the onset age of the propositi.

Diabetes was present in 231 (7.08 per cent) of the 3,262 parents of the propositi.

Parental consanguinity occurred in nine instances (0.55 per cent).

For the present series, there was no apparent tendency for diabetes to affect chiefly males in some pedigrees and chiefly females in others. The observed slight excess of like-sexed sib pairs and parent-offspring pairs is ex-

plicable on the basis of the sex ratio of diabetes in general.

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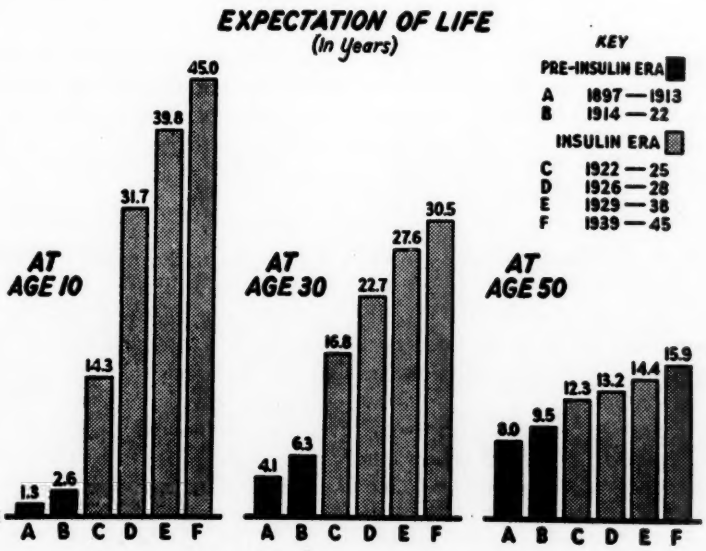

The increasing longevity of diabetics since the insulin era is shown in this chart based on the experience of the George F. Baker Clinic, Boston, Mass., during the years 1897-1945.

—from *The Facts of Life from Birth to Death*, by Louis I. Dublin, Ph.D. Copyright 1951 by The Macmillan Co., New York.

Effects of Acidosis
on Insulin Action
and on Carbohydrate
and Mineral Metabolism

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Among numerous factors in a long series of mutually aggravating metabolic derangements that are involved in the development and course of diabetic coma the state of acidosis *per se* has far reaching consequences in chemical pathology of the crisis and in disturbances of physiologic function. Acidosis, with lowered *p*H and "alkali reserve" of the body fluids, has numerous concomitant secondary effects. These interdependent effects include disturbances in normal activities of enzyme systems that are involved in many phases of carbohydrate and mineral metabolism, inhibition of insulin action, increased catabolism, and decreased anabolism in tissues.[1]

The following paragraphs summarize briefly several lines of investigation that have been carried out in this laboratory to elucidate some of the secondary metabolic derangements of acidosis. For brevity, references to methods employed and to the work of other investigators bearing on this subject are omitted here; such references may be found in the original articles in which these studies are reported more fully. Each separate effect of acidosis here defined may constitute an important additive factor contributing to the gravity of the crisis in diabetic coma. The data are assembled for the obvious purpose of stressing reasons for, and the importance of, quickly and judiciously correcting states of acidosis by appropriate measures as part of a rational plan for therapy

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AMMONIUM CHLORIDE ACIDOSIS

For the purpose of studying effects of a nonketonemic type of acidosis, apart from other complex factors that are involved in diabetic acidosis, severe acidosis was induced in fasting dogs by slow intravenous perfusion of M/6 solution of ammonium chloride solution. The perfusion was done by drip through a small plastic catheter into a jugular vein, over periods of from 2 to 4 days, using an apparatus that allowed the dog complete freedom of movement in a large cage.

This procedure induced a fairly constant pattern of chemical changes in the blood, illustrated by data presented in Table 1: decreased serum *p*H and carbon dioxide content, hemoconcentration (that is, increased volume of packed cells), a moderate increase in blood sugar with fasting levels increased from 74 to 99 mg./100cc., hyperchloremia, and a great decrease in concentration of organic acid-soluble phosphates in the cells.

TABLE 1 Averages of data on blood samples from 12 dogs in normal (fasting) states and with severe ammonium chloride acidosis, prior to insulin sensitivity and glucose tolerance tests.

Data Types	Units of Measure	Normal	NH_4Cl Acidosis
Serum pH		7.52	7.06
Serum CO_2 content	mEq./l.	23.1	6.3
Volume of packed cells	per cent	41.	52.
Blood sugar	mg./100cc.	74.	99.
Serum Cl	mEq./l.	107.	121.
Serum K	mEq./l.	4.3	5.6
Serum Na	mEq./l.	153.	150.
Serum inorganic P	mg./100cc.	3.2	3.9
Organic acid-soluble P in blood cells	mg./100cc.	46.0	25.2

The decreased concentration of organic acid-soluble phosphorus of the blood cells corresponds to changes found in the blood of patients in diabetic coma. The latter observations have been discussed at length in previous reviews.[2-4] It is sufficient to note here that there is evidence that this decrease reflects to a considerable degree the state of the labile stores of similar phosphorus compounds in other tissues of the body. In human patients, during the development of diabetic coma and during recovery therefrom, changes in the concentration of organic acid-soluble phosphorus and of potassium in the blood cells, decreasing in acidosis and increasing with recovery, are closely parallel. In dogs, the erythrocytes contain very little potassium and that relationship therefore could not be traced in these experiments.

ACIDOSIS INHIBITS INSULIN ACTION

There has been reported in older literature much evidence that in patients treated for diabetic coma the action of insulin was inhibited by conditions of ketonemic acidosis and that insulin action was favorably influenced by the administration of alkali to correct the acidotic state (see Reference 1, page 640). But under conditions of diabetic acidosis many complex factors are involved, each of which may be more or less responsible for failure or inhibition of insulin action. For an experimental approach to this problem, as stated above, ammonium chloride acidosis was chosen as a nonketonemic type of acidosis the effects of which could be studied apart from other factors recognized as playing a role in diabetic subjects.

Insulin sensitivity tests were performed on nondiabetic dogs in normal states and in states of severe acidosis induced by slow intravenous perfusion of M/6 ammonium chloride solution 2 to 4 days.[5] The tests included parallel determinations of blood sugar, plasma K and inorganic P, before and at suitable intervals during the first 3 hours following the intravenous injection of standard doses of insulin. In normal nonacidotic states the changes of blood sugar induced by insulin were closely paralleled by changes in concentration of plasma K and inorganic P, all three values sharply decreasing in the first 30 to 60 minutes and then returning to initial levels. In severely acidotic dogs, standard doses of insulin administered intravenously produced less fall in the concentration of blood sugar, with slower rate of fall and slower recovery to initial levels during the 3-hour test period than in the same dogs in nonacidotic states, while levels of plasma K and inorganic P tended to change very little or to remain stationary.

Figure 1 illustrates the results of some experiments performed to determine the effects of acidosis in a dog with alloxan-induced diabetes. The graphs represent data from three insulin sensitivity tests. The first was done with the dog in a normal (fasting) state before diabetes was induced, and the second several days after diabetes was induced by the intravenous injection of alloxan; the plasma *p*H was normal in both instances. The third test was done on the diabetic dog after severe acidosis was induced by continuous intravenous perfusion of M/6 ammonium chloride solution for 70 hours. In the first two tests the standard dose of insulin provoked the same percentile fall in concentration of blood sugar in the first 20 minutes following the injection of insulin; values for plasma K and inorganic P fell concomitantly during 40 minutes and then rose, somewhat more slowly in the diabetic state. In the third test, done in the presence of severe acidosis with serum carbon dioxide content reduced to 7 mEq./L. and with the serum *p*H 7.08, the blood sugar fell much less and rose more slowly in the third hour, while levels of plasma K and inorganic P remained practically stationary.

Thus, conditions of acidosis in normal and in alloxan-diabetic dogs appeared to inhibit the action of insulin by interfering with processes of phosphorylation that are involved in the concomitant cellular uptake of sugar, potassium and phosphorus from the plasma.

ACIDOSIS LEADS TO DECREASED GLUCOSE TOLERANCE

As an extension of the studies on the effect of acidosis on insulin action, intravenous glucose tolerance tests with parallel determinations of blood sugar, plasma K and inorganic P were done on dogs in normal (fasting) states and in states of severe acidosis similarly induced

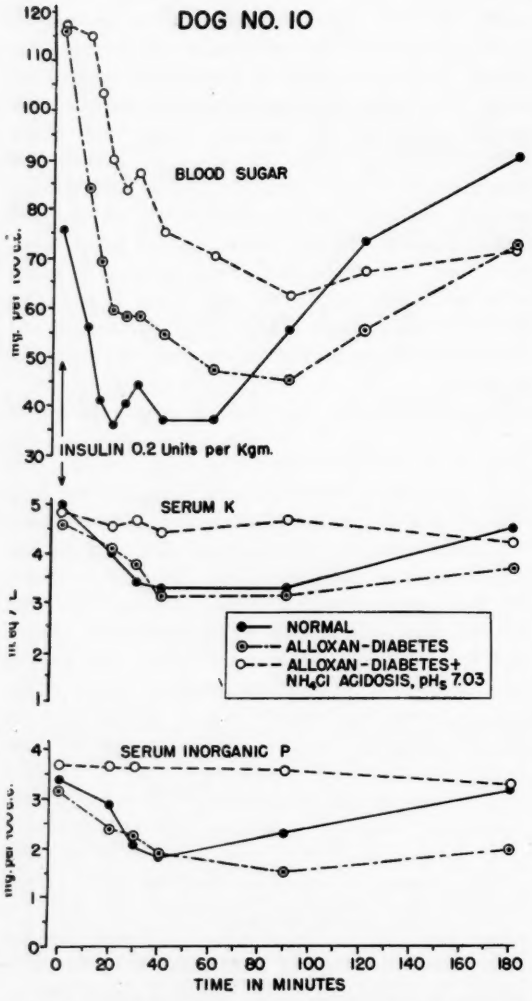
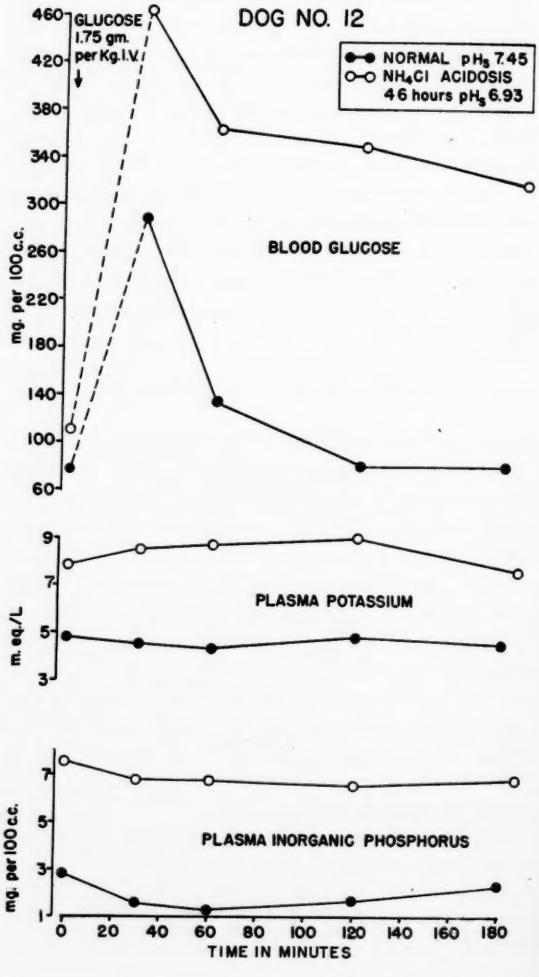


FIGURE 1 Insulin-sensitivity tests in a dog before and after diabetes was induced by alloxan, and in the alloxan-diabetic dog in severe acidosis induced by intravenous perfusion of ammonium chloride solution.

by intravenous perfusions of ammonium chloride solution.[6] Figure 2 illustrates the pattern of changes observed in one of these experiments. Following the standard dose of glucose administered intravenously (1.75 gm./kg. of body weight, in 50 per cent solution), the blood sugar rose to 280 mg./100 cc. and fell to its original level in 2 hours. After a severe state of acidosis was induced, with serum *p*H 6.93, the same dose of glucose produced a higher rise in level of blood sugar, followed by a slow fall during the 3-hour period of the test. During the first test, done in the nonacidotic state, the plasma inorganic P fell from 3 to 1 mg./100 cc. and the plasma K remained unchanged. During the development of acidosis both the plasma K and inorganic P rose considerably above normal, higher than observed in most of these experiments; during the glucose tolerance tests, the plasma inorganic P remained stationary while the potassium increased slightly. This blood sugar curve was the most "diabetic" in type of any observed in the series of experiments on 5 dogs reported.[6] Such findings again support the thesis that states of acidosis inhibit cellular uptake of sugar from the blood.

FIGURE 2 Glucose tolerance tests in a dog in normal (fasting) state and with severe ammonium chloride acidosis.



ACIDOSIS INHIBITS THE UPTAKE OF SUGAR BY EXTRAHEPATIC TISSUES

To study the uptake of sugar from the blood by extrahepatic tissues, apart from insulin action, dogs were completely eviscerated and levels of blood sugar were determined at suitable intervals following the operation. Experiments were done thus on normal (nonacidotic) dogs and on dogs that had been made severely acidotic by continuous intravenous perfusion of M/6 ammonium chloride solution during 60 to 70 hours before the operation.[7] Figure 3 illustrates the average changes in blood sugar levels (that is, the rates of disappearance of sugar) immediately after evisceration in 3 nonacidotic (control) dogs and in 3 severely acidotic dogs. Average serum *p*H values in the control animals immediately before operation was 7.32 and in the acidotic animals 6.98. The graphs, representing averages of the blood sugar levels expressed as percent of initial concentrations, show a much slower rate of disappearance of blood sugar in the acidotic than in the nonacidotic eviscerated dogs. In previous experiments a similar difference had been observed in rates of disappearance of blood sugar in hepatectomized dogs, acidotic and nonacidotic, but under such conditions the differences might have been ascribed to interference with insulin action or with insulin production by the intact pancreas;[8] consequently, those preliminary experiments were extended to studies on eviscerated animals so as to observe rates of disappearance of blood sugar in the absence of the pancreas.

Thus in completely eviscerated dogs immediately following operation, a slower disappearance of blood sugar in acidotic than in nonacidotic animals indicates that acidosis inhibits the uptake of sugar by extrahepatic tissues, apart from insulin action.

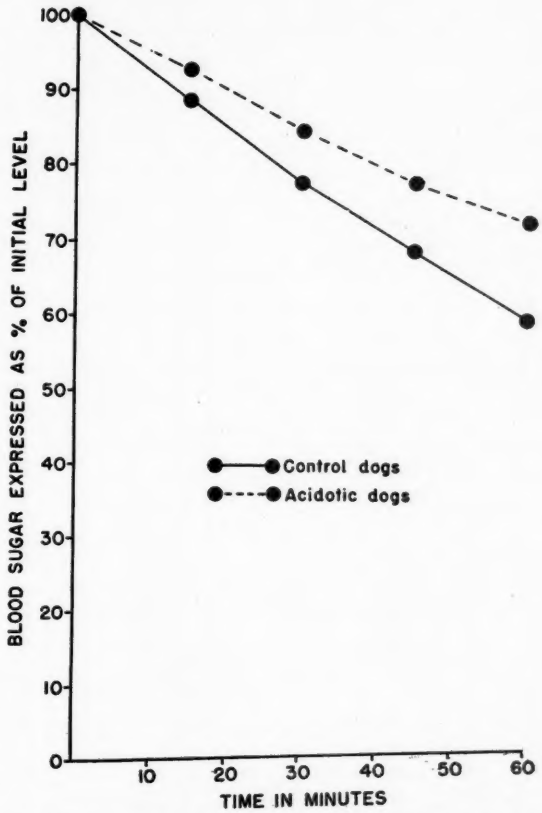


FIGURE 3 Disappearance of sugar from the blood in 5 dogs completely eviscerated in normal non-acidotic state and in 5 dogs eviscerated after severe acidosis was induced by perfusion with ammonium chloride.

ACIDOSIS INHIBITS GLYCOLYSIS BY BLOOD CELLS

The significance of blood glycolysis in the general (total) metabolism of the body has been much debated since the days of Claude Bernard. While blood glycolysis in vivo constitutes a relatively small part of the total carbohydrate metabolism of the body, the changes in rate of blood glycolysis that occur under varying physiologic and pathologic conditions may offer important indices of parallel rates of glucose utilization in other tissues of the body which are quantitatively more important. Hsu[9] presented evidence that blood glycolysis in vivo may contribute a large portion of blood lactic acid during rest, concluding that "this source alone would seem likely to keep the cycle of lactic-acid-liver-glycogen-blood sugar in continuous operation." Hsu showed, moreover, that in natural conditions the blood vessels exhibit glycolysis, producing lactic acid at the expense of blood sugar. The rate of glycolysis measured in blood in vitro at 37°C, with normal cell content, normally amounts to around 15 mg. loss of glucose per hour per 100 cc. of blood, equivalent to a rate of 3.6 grams of glucose per liter per day. For an average adult this rate normally would account for 15 to 20 grams of glucose per day destroyed by blood glycolysis alone, a small but not insignificant quantity. In febrile conditions, especially with leucocytosis, this rate may be more than quadrupled.

In order to study various factors that affect glycolysis in blood, including changes of *p*H, we have devised a technique which permits separate estimations of rates of glycolysis in red and white cells, employing varying

mixtures of the two types of cells in their own plasma. We have applied this technique to studies of glycolysis in human and dog blood, at normal *p*H and after acidification in vitro, and in blood drawn from dogs in states of severe acidosis induced by prolonged intravenous perfusions of ammonium chloride solution.[10]

In heparinized blood of normal dogs, at 37° C and normal *p*H, glycolysis averaged 0.018 micrograms of glucose disappearance per hour per million red cells and 9.9 micrograms per hour per million white cells. Thus the rate for the white cells was 500 to 600 times faster than that of the red cells. In acidotic blood the rate of glycolysis was inhibited, more in the erythrocytes than in leucocytes. In four samples of dog blood with *p*H around 7.0, the rates of glycolysis for red and white cells respectively averaged 0.006 and 6.0 micrograms per hour per million cells. Correction of the *p*H values to normal by the addition of sodium bicarbonate restored the rates of glycolysis to normal, in both red and white cells.

Figure 4 illustrates the results of one of the experiments done in this series of studies, with measurements of glycolysis in divided samples of whole blood from a dog with severe acidosis induced by intravenous perfusion of ammonium chloride M/6 solution. The graphs indicate, first, a relatively slow rate of glycolysis in the blood as drawn, with plasma *p*H 7.11, and second, a faster rate in the same blood after the addition of sodium bicarbonate brought the plasma *p*H to 7.40.

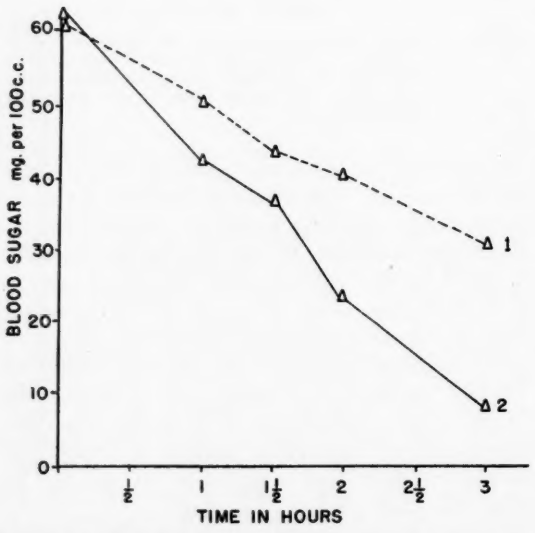


FIGURE 4 Glycolysis in blood drawn from a dog with ammonium chloride acidosis: 1) Blood at pH 7.11, as drawn, and 2) readjusted to pH 7.40 by the addition of $NaHCO_3$ in vitro.

Data gathered in recent experiments (to be published) indicate that changes in glycogen and pyruvate levels and rates of oxygen consumption of blood are very small during glycolysis and apparently are not significantly different in blood with normal and low *p*H; moreover, the ratio between glucose disappearance and lactic acid formation as an end-product of glycolysis seems to be the same in normal and in acidotic blood. Correlated studies done on yeast hexokinase have yielded evidence that the glucose-phosphorylating activity of hexokinase is inhibited at a low *p*H. Further studies are being carried on to determine the effects of *p*H on the activity of hexokinases of blood cells and of other animal tissues.

The results of these studies strongly suggest that acidosis interferes with glycolysis by inhibiting the initial phosphorylation of glucose (probably an effect on hexokinase) rather than by affecting enzymatic reactions in later stages of the glycolytic cycle.

ACIDOSIS INCREASES CELLULAR CATABOLISM

Metabolic balance studies on human diabetic subjects deprived of insulin have yielded much evidence that the development of acidosis is attended with large urinary losses of water and electrolytes, labile intracellular constituents, especially N, P and K.[11, 12] In their early study, Atchley, Loeb, and others[11] showed that such losses began before the actual development of noteworthy acidosis. Negative metabolic balances at that period may be ascribed to a lack of the anabolic effects of insulin. But a corollary of this situation should be emphasized: namely, that with progressive development of ketosis the state of acidosis, increasing in severity, rapidly accelerates the losses. This point has been emphasized in a recent report on metabolic studies done on alloxan-diabetic rats.[13]

Rats with severe diabetes induced by intravenous injections of alloxan, eating a standard diet ad libitum and receiving 1 and 2 units of protamine zinc insulin daily, maintained constant body weight, nitrogen and mineral balance, while excreting 0.5 to 1.5 gm. of glucose per day, without ketonuria. When insulin and food were withheld they quickly developed ketosis and died in severe acidosis, usually within 2 to 4 days, with a rapid increase in urinary excretion of N, P and K, leading to gross metabolic deficits. When allowed food after the insulin was withheld some of the rats overate, doubling their usual daily food intake. These rats ex-

creted large amounts of sugar (as high as 10 gm. per day) and a volume of urine sometimes equal to their weight. They progressively lost weight, of course, but some survived as long as 30 days without ketosis and at no time showed the abrupt development of large mineral and N deficits that occurred so quickly in the fasted acidotic rats.

Such observations indicate that in diabetic rats and presumably in human diabetic subjects the progressive development of ketonemic acidosis is a critical factor hastening metabolic losses of nitrogen and minerals, rapid loss of body weight, dehydration and death.

A corollary to this point is offered by the metabolic studies reported by Greenman and associates[14] on diabetic patients in severe acidosis and during recovery while being treated with insulin, saline and glucose solutions. In addition to demonstrating anew the high urinary losses that characterized the acidotic state before treatment was started, the investigators stated that "potassium continued to pour out of the cells throughout these earlier hours of therapy." Losses of P and K in the urine that continue after the start of insulin therapy may properly be ascribed to the uncorrected state of acidosis. The losses diminish abruptly after acidosis is corrected and cease after insulin action becomes fully effective, reestablishing normal anabolic processes.

Knowledge of intracellular changes, previously based largely on indirect evidence obtained from metabolic balance studies, has been amplified recently by direct analyses of tissues (muscle, liver, heart, erythrocytes) of alloxan-diabetic rats with severe ketoacidosis. A preliminary report of this study[15] presented data indicating that in muscle of acidotic rats, compared with normal controls, the concentration of water and potassium decreased and the concentration of nitrogen increased slightly, with values for sodium and chloride showing no significant change. In liver there was a gain of water, sodium and nitrogen, with no change in concentration of chloride or potassium. The finding in the acidotic rats of a higher than normal nitrogen content in liver and muscle, relative to the total solids, appeared to be in accord with the concept that acidosis leads to a greater loss of labile nonprotein constituents than of protein from body tissues. Further analyses, not included in that preliminary report, show the average concentration of potassium in the erythrocytes, 109 mEq./L in the normal controls, reduced to 89.5 mEq./L in the rats with ketoacidosis. This reduction of erythrocyte potassium corresponds to observations on human patients in diabetic coma reported earlier[3, 4] and supports the thesis that the reduction in erythrocyte potassium may constitute a valuable index of the state of labile potassium stores in other tissues.

DISCUSSION

What has been presented here merely supports and corroborates the conclusions already drawn from clinical and experimental observations by many other investigators who have recognized the critical importance of the factor of acidosis in diabetic coma and who concluded therefore that recovery could be hastened by the judicious administration of alkali to correct acidosis quickly in treating the comatose diabetic patient.[1] It is especially pertinent to add here, as a further argument favoring this thesis, the important observations of Kety and coworkers[16] who found that in diabetic comatose patients lowered *p*H of the blood was closely correlated with diminishing cerebral oxygen uptake, which in turn was an important prognostic index of mortality in their large series of cases. These investigators emphasized the potential benefit of correcting the acidotic state quickly by the administration of alkali, pointing out that intravenously injected doses of sodium bicarbonate only sufficient to raise the blood carbon dioxide content by 10 or 15 volumes per cent was sufficient to bring the *p*H of the blood to normal.

SUMMARY

Studies on dogs with severe acidosis induced by intravenous perfusion of ammonium chloride solution, and on alloxan-diabetic rats with severe ketonemic acidosis, have been reviewed and the results interpreted in relation to analogous observations on human subjects in diabetic coma. The results of the experimental studies indicate that states of acidosis *per se,* with lowered *p*H and alkali reserve of the body fluids, lead to mild hyperglycemia, hemoconcentration, losses of intracellular labile phosphates and potassium, inhibition of insulin action, decreased glucose tolerance, inhibition of the uptake of glucose from the blood by extrahepatic tissues, and inhibition of blood glycolysis. Each separate metabolic effect of acidosis thus demonstrated may constitute an important factor contributing to and aggravating the gravity of a diabetic crisis in human patients.

ACKNOWLEDGMENTS

The work reported in this paper has been aided by grants from the Nutrition Foundation, Inc., and the Life Insurance Medical Research Fund.

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DISCUSSION

DR. T. S. DANOWSKI (*Pittsburgh*): I should like to ask Dr. Mackler and his co-workers: Can the drop in carbohydrate tolerance demonstrated during acidosis be completely reversed merely by giving insulin? From the practical viewpoint, that would be very important.

The question of whether or not alkali should be used in the early therapy of acidosis in coma is one that cannot be answered categorically. It has been our custom not to give alkali, and we have seemed to get perfectly reasonable results.

The authors suggested that possibly acidosis and loss of carbohydrate tolerance accelerated and contributed to the negative balances of potassium. I think it is right to point out that deficits in potassium in diabetic acidosis occur for a wide variety of reasons. Initially, there is starvation and usually vomiting and, of course, the excretion by the kidneys is increased by adrenal-cortical activity and certainly by dehydration. With this variety of mechanisms contributing to the over-all balance of potassium; acidosis, if it is a factor, would primarily affect the rates of recovery.

DR. GEORGE THORN (*Boston*): These are very interesting observations. I wonder if the theory concerning the mode by which acidosis acts—namely, interference in the early steps of phosphorylation—might be checked by studying utilization of fructose with or without acidosis. I wonder whether the authors have made any attempt to check on this particular point.

DR. BRUCE MACKLER (*Cincinnati*): In regard to Dr. Danowski's question as to whether insulin will reverse the inhibitory effect of acidosis, we have not attempted to study this in vivo. We do plan to do similar types of work in vitro at a later time. Also, I did not intend to say that acidosis was the only factor that would produce losses of electrolytes during diabetic crisis.

Regarding fructose utilization during acidosis, we have done some preliminary work which is not completed at the present time. In dogs made acidotic with ammonium chloride, we found that results of fructose tolerance tests were the same as results of tests performed during normal control states. In other words, there was no effect of acidosis on the utilization of fructose by the intact animal.

In studies of blood glycolysis, now in progress, it appears that there is no specific fructokinase in blood; the rate of utilization of fructose by blood, in the absence of glucose, is inhibited in acidotic blood to the same degree as is glucose.

A Survey of Tuberculosis Among Diabetics

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Both in the literature and as a matter of clinical experience, there has been a general impression that diabetics have an increased susceptibility to tuberculosis. The largest study in the literature is that of Root,[1] who obtained roentgenograms on 1659 consecutive diabetic patients between 1927 and 1930.

The present study was launched as a joint project of the Philadelphia Tuberculosis and Health Association and of the Philadelphia County Medical Society, with a committee of 14 specialists representing the fields of tuberculosis, roentgenology and diabetes. This paper is a condensation of the full report recently published, which consists of 50 pages, including 56 tables.[2]

From December 1945 through February 1947, diabetics were interviewed and data were recorded on two questionnaires—one during the patient interview and the other by the private or clinic physician. The diabetics were x-rayed at two units and the films mixed with those of many hundreds of nondiabetics being routinely surveyed. Two of us (K.R.B. and D.A.C.) interpreted every film of the diabetics and each was unaware whether the film being interpreted was of a diabetic or of a nondiabetic. There was no possibility of any unconscious bias.

ANALYSIS OF THE CASES SURVEYED

Of 3167 individuals submitted by 22 diabetes clinics and 95 private physicians, 3106 satisfied the committee's

Presented at the Annual Meeting of the American Diabetes Association, Chicago, June 8, 1952.

criteria for diabetes. 82.6 per cent of the cases were from the 22 hospital clinics and 17.4 per cent were referred by the 95 private physicians. The prevalence of tuberculosis among the clinic patients and among the private patients was practically the same, 8.3 per cent and 8.9 per cent, respectively.

Among the items of information collected were the severity of the diabetes as measured by the amount of insulin taken, the duration of the diabetes, control of the diabetes, age at survey, age at onset of diabetes, sex, race, per cent standard weight, history of coma, history of gangrene and amputations, history of boils and carbuncles, history of pleurisy, history of contact with tuberculosis, presence of survey tuberculosis, presence of active tuberculosis, stage of tuberculosis, site of tuberculosis, site of cavities. These data were transferred to punch cards and the statistician produced over 100 tables, each table correlating two, three or more items. In this large number of tables it was necessary to seek for some order and meaning.

AGE, SEX AND RACE

The distribution of the 3106 diabetics by age, sex and race is shown in Figure 1. The group was preponderantly older, female and white. There were 430 individuals younger than 40—14 per cent of the total and hereafter we shall refer to these as the younger group. 86 per cent were 40 or older. 30.7 per cent were males and 69.3 per cent were females. There were 861 nonwhites, 27.7 per cent of the whole diabetic group. The nonwhite population of Philadelphia was estimated to be 14.5 per cent. It will be noted that the peak of the nonwhite members is about a decade earlier than for the whites, probably due chiefly to the shorter expectation of life of the nonwhites in the general population.

COMPARISON WITH CONTROL GROUP

The first problem which needed to be investigated was how the prevalence of tuberculosis in the diabetic group compared with the prevalence in the general population. While it was not an ideal control group, 71,767 apparently healthy Philadelphia industrial workers who had been surveyed between October 1942 and May 1945 were used (Figure 2). This large group was broken down into subgroups to correspond to the distribution by age, sex and race of the diabetic group. The prevalence of tuberculosis in the industrial group thus adjusted was 4.3 per cent. Of the 3106 diabetics 261 were found to have tuberculosis. This is a prevalence of 8.4 per cent, nearly double that of the in-

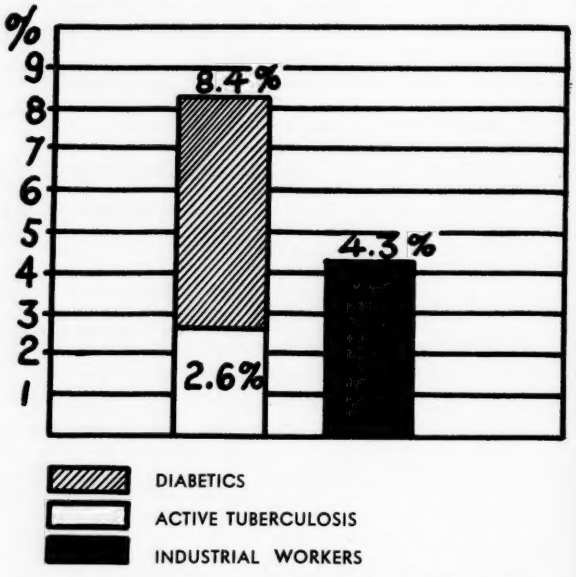

FIGURE 2 Prevalence of tuberculosis in diabetics and in industrial workers (adjusted)

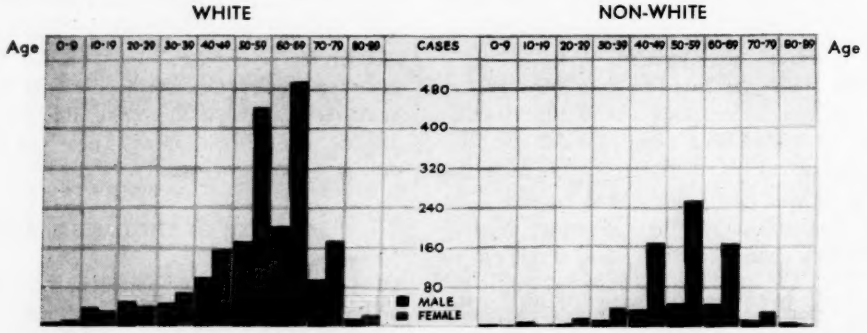

FIGURE 1 Age, race and sex distribution

dustrial group. 80 cases were classified as active tuberculosis, a prevalence of 2.6 per cent. The prevalence of total survey tuberculosis in the general population is known to increase markedly with advancing years. To a small extent this was found to be true in the diabetic group.

There was more than twice as much survey tuberculosis among the white diabetics as among the Negroes —almost 10 per cent contrasted with 4.3 per cent. Surveys of the general population have also shown a higher figure for whites. However, the tuberculosis mortality rate of the general population of Philadelphia was more than five times greater for Negroes than for whites. Presumably, tuberculosis runs a more acute course in the Negro diabetic and many do not live long enough to be counted in a survey.

Almost twice as much tuberculosis was found in male diabetics (12.3 per cent) as in female diabetics (6.7 per cent).

THE INFLUENCE OF SEVERITY OF DIABETES

While we were studying certain diabetes factors in relation to the increased tuberculosis prevalence among diabetics, we noted that tuberculosis read as "probably active" seemed more relevant than did total tuberculosis. Probably fibrocalcific and strand-like lesions often antedated the diabetes.

The prevalence of active tuberculosis was 2.6 per cent in the whole group. Of course, it occurred to us at once that the severity of the diabetes as measured by the amount of insulin taken might have something to do with the prevalence of active tuberculosis, and indeed this proved to be the case. In Figure 3 one will notice that the prevalence of active tuberculosis is approximately twice as great in the younger group as in the older group. One will notice, too, that when the patient is taking 41 units of insulin and upward (severe group) the prevalence of active tuberculosis for both the younger and older diabetics is about three times as great as in the mild and moderate cases.

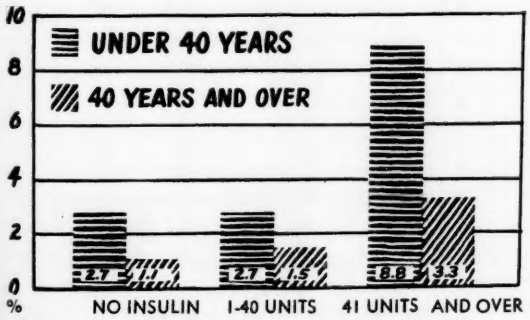

FIGURE 3 Prevalence of active tuberculosis by severity of diabetes and age

When one considers the relationship between severity of the diabetes and the prevalence of total survey tuberculosis in the younger age group, the same increase of prevalence with increase of severity obtains. In the older age group, however, there is so much old inactive tuberculosis in all three degrees of severity that no clear relationship of prevalence and severity can be demonstrated.

THE INFLUENCE OF DURATION OF DIABETES

One would think that the duration of the diabetes might be a contributing factor to the prevalence of active tuberculosis. In Figure 4 it is shown again that the prevalence of active tuberculosis is greater in the younger group than in the older group. It is also shown that when duration of under 10 years is compared with duration of 10 years and over in the younger group, there is a marked increase of prevalence from 3.2 per cent to 11.4 per cent. In the older group there is no such increase; in fact, there is slight decrease. When total survey tuberculosis is considered, the same relationships are found. The prevalence of survey tuberculosis in the younger group with duration of 10 years and over was 16.7 per cent.

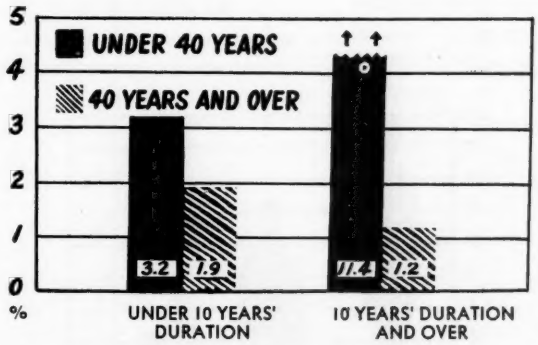

FIGURE 4 Prevalence of active tuberculosis by duration of diabetes and age

THE INFLUENCE OF A HISTORY OF DIABETES COMA

It was anticipated that the degree of control of the diabetes might prove to be an important factor in the prevalence of tuberculosis. To estimate control one should have available a whole body of information which it was impossible to collect. Furthermore, phy-

sicians are by no means in accord as to what standards constitute good control.

It was impossible to draw any valid conclusions regarding the relationship of tuberculosis to our observations of blood sugar levels. However, another approach to the problem of diabetes control is through a study of a history of coma, the end result of the disease when uncontrolled. Of the group under age 40, approximately 39 per cent had been in coma one or more times and 61 per cent had had no coma. Of the older group, age 40 and over, only 13 per cent had had coma. In Figure 5 is shown the prevalence of active tuberculosis in the younger and older groups, with and without coma. As in the previous figures, the prevalence of active tuberculosis is much higher in the younger group. But in the younger group the prevalence of active tuberculosis with coma is only a little higher than without coma, 6.0 per cent compared with 4.7 per cent; and in the older group the prevalence is slightly lower when coma is present, the figures being 1.4 per cent with coma and 1.6 per cent without coma. When total tuberculosis is considered in the younger group the prevalence is 9.6 per cent with coma and 5.8 per cent without coma; in the older group 6.9 per cent with coma and 8.2 per cent without coma. When the younger group only is considered, it would seem that a history of coma does have a slight influence in increasing the prevalence of tuberculosis, probably because cases of diabetes which get coma as a whole are more severe, or less well controlled, than those which do not.

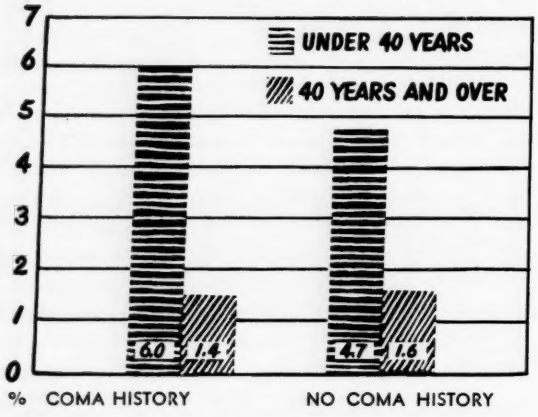

FIGURE 5 Prevalence of active tuberculosis by coma history

THE INFLUENCE OF BODY WEIGHT

It has long been recognized that obesity predisposes to diabetes; in like manner thinness predisposes to tuberculosis. It seemed, therefore, that it would be of interest to study the relationship between standard weight and the prevalence of tuberculosis in the diabetic. In Figure 6 the prevalence of total tuberculosis is compared in diabetics and in industrial workers, each divided into groups of underweight, standard weight and overweight. In both the diabetics and industrial workers tuberculosis was twice as prevalent in the light weights as in the heavy weights. It will be noted, too, that the prevalence of tuberculosis is much larger in the diabetics than in the industrial workers.

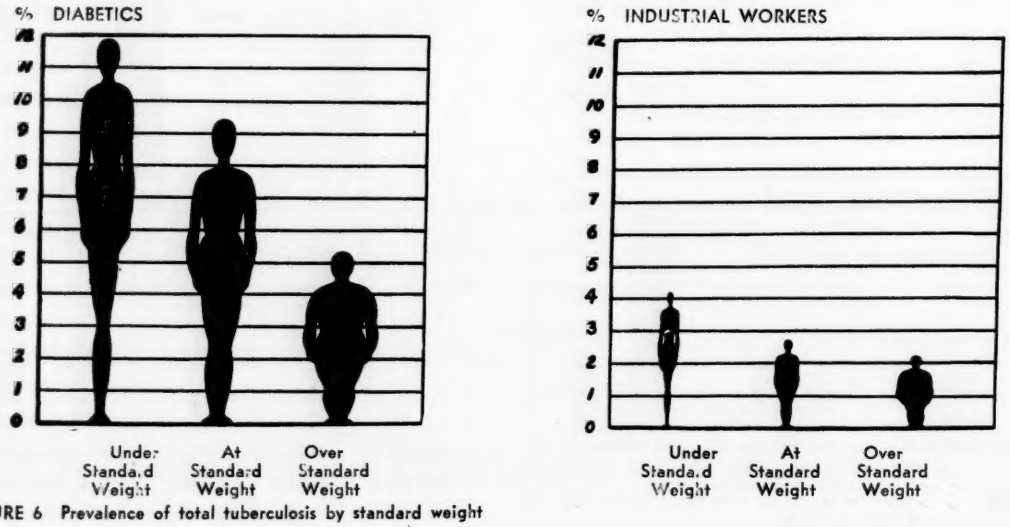

FIGURE 6 Prevalence of total tuberculosis by standard weight

When we study the prevalence of active tuberculosis by age and standard weight, as is done in Figure 7, it will be noted that weight makes a great difference in the prevalence of active tuberculosis in both age groups, the figures being 6.2, 6.7 and 3.0 per cent for the younger group, and 3.9, 1.4 and 0.7 per cent in the older group. Figure 7 also shows that the younger group has three times as much active tuberculosis as the older group—5.3 per cent compared with 1.7 per cent.

This marked influence of the weight factor was found to be present throughout the whole study, no matter what other factors were correlated with the weight factor. Because of the emphasis which has been generally put on control of overweight in the treatment of diabetes, it might be well to point out that underweight very distinctly adds to the hazard of tuberculosis. This is true at all ages but particularly in the younger group. The hazard also increases as the severity and the duration increase.

There was twice the prevalence of active tuberculosis in the 298 patients with a history of contact with tuberculosis as in those without such a history. There was also twice the prevalence of active tuberculosis in the 457 cases with a history of pleurisy as in those without such a history.

There was no marked difference in the prevalence of tuberculosis in diabetics having histories of gangrene or amputations, which merely means that increased prevalence of arteriosclerosis in diabetics does not have any obvious relation to increased susceptibility to tuberculosis. Nor did a history of boils and carbuncles have any effect on the prevalence of tuberculosis, indicating that the increased susceptibilities of diabetics to tuberculosis and to pyogenic infections are hypersusceptibilities having nothing in common which can be demonstrated.

THE NATURE OF THE PULMONARY LESIONS

We were interested in possible differences between diabetics and nondiabetics as regards extent of disease, site of lesions, and impression of activity. We therefore obtained a matched sample of nondiabetics whose films had been read as showing tuberculosis during the same general time period. The percentage of minimal disease was about 70 per cent in both groups. However, there was no pleural effusion in the comparison group while there were three pleural effusions and one tuberculous pericarditis among the diabetics. Only one individual had an active primary tuberculosis in the comparison group whereas there were three in the diabetic group, suggesting hypersensitivity among the diabetics.

There is a clinical impression that tuberculosis in the diabetic is characterized by mid-lung and basal lesions. We studied site of tuberculosis lesions in the diabetics

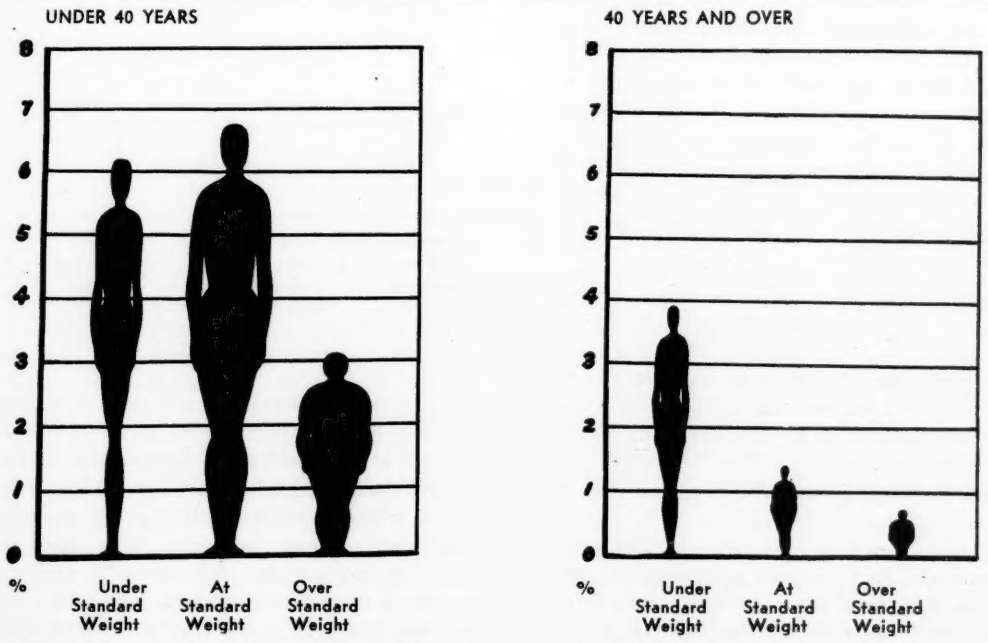

FIGURE 7 Prevalence of active tuberculosis by age and standard weight, in diabetics

TABLE 1 Proportion of active cases of tuberculosis among diabetics compared with those in a comparison group

Stage	Diabetics			Comparison Group		
	Total Number	Number Active	Per Cent Active	Total Number	Number Active	Per Cent Active
Minimal	165	15	9.1	184	6	3.3
Advanced	85	58	68.2	59	21	35.6
Pleural, pericardial and active primary	11	7	63.6	7	1	14.1
	261	80	30.6	250	28	11.2

and in the comparison group. Since serial films were not available, an attempt was made to gauge the site of origin by excluding all cases with involvement of more than one lung third.

The proportion of tuberculosis found in the lower two-thirds was higher in the diabetics than in the matched sample. However, this was due to the higher proportion of active tuberculosis among the diabetics. When active tuberculosis alone was considered there was no difference between the diabetics and the sample. The clinical impression of increased basal tuberculosis among diabetics may be due to their older age.

While it is impossible to evaluate tuberculosis activity on the basis of one film, the presence of definite cavitation or extensive soft mottling can somewhat justifiably be interpreted as indicating a "probably active" condition.

The films of 31 per cent of the tuberculous diabetics were read as probably active, which is a percentage three times higher than the figure for the comparison group. The increased proportion of active cases was maintained in all stages and in both races (Table 1 and Figure 8).

There is a clinical impression that tuberculosis in the diabetic runs a more acute course than in the nondiabetic. While a follow-up study on our tuberculous diabetics is now under way, no systematic data are yet available.

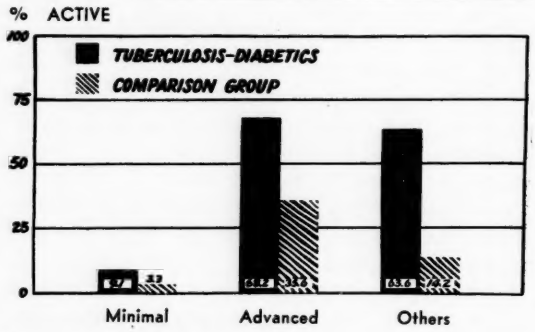

FIGURE 8 Activity by stage of disease

SUMMARY

1. The prevalence of tuberculosis in cases of diabetes was found to be 8.4 per cent, compared with 4.3 per cent in an industrial group adjusted to correspond in age, sex and race.

2. The tuberculossi was active in 2.6 per cent of the diabetics.

3. Active tuberculosis was three times as prevalent in those under 40 years of age as in those 40 and over.

4. The prevalence of active tuberculosis increased markedly with the severity of the diabetes.

5. In the younger age group the prevalence of active tuberculosis was much greater in those having had diabetes ten years or more.

6. The prevalence of tuberculosis was much greater in underweights than in overweights.

7. Tuberculosis was much more likely to be active in diabetics than in nondiabetics.

ACKNOWLEDGMENT

The cost of the investigation reported herewith was borne by the Philadelphia Tuberculosis and Health Association.

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DISCUSSION

DR. JOSEPH B. STOCKLEN (*Cleveland*): Any investigation into influences affecting the course of tuberculosis requires a large number of observations on an adequately controlled group. Dr. Dillon and his associates appear to have a sufficiently large group of patients in their study to yield statistically valid results. There might be some criticism of the use of a control group consisting of industrial workers. It is quite probable that this group was of higher economic status than the diabetic group, most of whom were clinic patients. How-

ever, it is doubtful that this factor would account for the rather large difference in the prevalence of tuberculosis between the two groups.

This extensive study, coupled with the work of other investigators, leaves little room for doubt that tuberculosis is more prevalent among diabetics than nondiabetics and that it is also more serious. In regard to no other complicating condition, with the possible exception of silicosis, is there better evidence of hazard to the tuberculous patient. Therefore it would seem that a routine chest roentgenogram, at possibly six month intervals, should be included in the management of every case of diabetes.

As a suggestion, it is hoped that some investigator may become interested in an experiment parallel to that reported in 1950 by Vorwald in relation to silicosis. He found that guinea pigs having silicosis succumbed to tuberculosis after inoculation with BCG. Organisms obtained at necropsy were then inoculated into normal guinea pigs. These animals survived, indicating that the fatal tuberculosis in cases with silicosis depended on the decreased resistance of the host, rather than on increased virulence of the organism.

DR. ELLIOTT P. JOSLIN (*Boston*): First of all, I want to show my pleasure and extend my congratulations to Dr. Dillon for his beautiful charts. I think they represent an example that would be fine for all of us to follow.

I have just one new figure on tuberculosis which has not been reported. Among 656 diabetics who have died in the last two years, 0.9 per cent died with tuberculosis. That is the lowest figure we have ever had. Of course, 656 deaths is not great among 12,000 diabetic deaths. The tuberculosis percentage has been between 4 and 5 per cent; in the last ten or fifteen years it has dropped to between 2 and 3 per cent, and now to 0.9 per cent. When one thinks of how half of the diabetics at the beginning of the century died with tuberculosis, the change is wonderful.

DR. EDWARD S. DILLON (Closing): I wish to thank Dr. Stocklen and Dr. Joslin for their comments.

Of course, this study has a disadvantage inasmuch as it was a survey of incidence and not a study of mortality. We hope to follow up this survey. We have already set the wheels in motion to survey these patients again after a period of five or six years, to see what has become of them.

As Dr. Joslin pointed out, the mortality from tuberculosis in diabetics in general is relatively small. Nevertheless, in a small select group, namely the young patients who are underweight, the dangers of tuberculosis are still quite large.

INSTRUCTIONS FOR PATIENTS

One of the commonest complaints voiced by patients concerns the failure of their physicians to provide adequate instructions to follow after they leave the offices of the physicians. These patients complain that sometimes they think they must be clairvoyant to do what their doctors expect of them. Even those who seem to expect only general directions often mildly voice a suggestion that the medical profession be more explicit when instructions are given to someone who is ill or to his relatives. If prescriptions for drugs can be written in detail so can other instructions, say these critics. . . .

Any act that convinces people that the patients' comfort and health are always uppermost in the thoughts of physicians will do much to offset the statements of those who wish to pervert the thinking of persons receiving medical care.

—From an editorial in *The Journal* of the
American Medical Association, October 20, 1951.

Present Status of New Insulin Modifications

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Since the discovery of protamine insulin by Hagedorn[1] and its introduction into clinical usage in 1936, there has been a constant stream of modifications of insulin having the common attribute of prolonged action by virtue of differences in solubility in tissue fluids at the approximate *p*H of the body. In general, such modifications have been prepared according to the original principles laid down by Hagedorn, utilizing combinations of insulin with protein precipitants described by him (protamines, histones, globins, kyrins) or by means of chemicals (hexamine, isocyanate, polyvinylpyrroladone) capable of altering solubility. The physical characteristics of such preparations vary from clear to cloudy suspensions, depending upon the occurrence of precipitation at various *p*H ranges. By varying the quantity of the agent used in proportion to the insulin, and the zinc content, or both, either in bulk or extemporaneously by mixing, the preparation of a wide variety of combinations having time activities ranging between the short, profound action of regular insulin and the long, slow effect of protamine zinc insulin is made possible.

All these preparations display the characteristic hypoglycemic action of insulin, but they differ from one another in rate of onset of action and duration of effect. Thus far, duration of action has never been obtained except at the expense of rapidity of onset. The selection of a given preparation for wide-scale use has, consequently, necessitated long-term and laborious clinical comparisons to establish the value of any specific time activity. Clinically, the major problem has been to determine which particular time activity best meets the average daily needs of the greatest number of diabetic patients.

CLINICAL REPORTS

The progress of these studies has been reviewed from time to time[2-6] during the last decade. More than a score of so-called intermediate acting preparations have been tested. They exert their greatest usefulness and display their most critical differences in timing in severe (unstable) cases of diabetes,[7] and their differences tend to be minimized and become unimportant in stable or mild cases. That controversial evidence of clinical differences

in timing between globin insulin with zinc and NPH insulin exists[7-10] is doubtless the result of choice and number of cases subjected to critical analysis. The statistical data compiled by Izzo[7] seems incontestable in this connection and, furthermore, the clinical impressions of longer duration of action of NPH insulin have been borne out by the Toronto assay curves published by Jamieson, Lacey, and Fisher[11] (Figure 1).

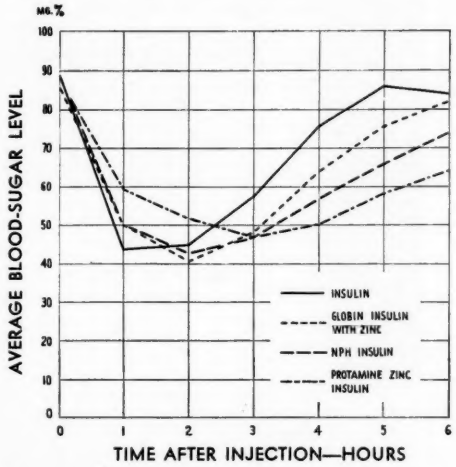

FIGURE 1 Average blood sugar levels in groups of 32 normal rabbits following the subcutaneous injection of the various insulin preparations as indicated. After Jamieson, Lacey and Fisher[11]

The most generally useful of these preparations have been those which have acted in the range exhibited by 2:1 admixtures of insulin and protamine zinc insulin. Many clinical reports[6-9, 12-17] substantiate the essential similarity of action of NPH insulin to 2:1 mixture. Since the clinical usage of NPH insulin has been widely broadened by its introduction on the market in 1950, further review of this more recent experience is presented at this time. The entire bibliography on this subject is far too large to include *in toto*, so for earlier references the reader should refer to the reviews already cited.

A number of recent reports on the comparative effectiveness of NPH insulin have appeared in the literature. Baganz and associates[18] studied 41 patients hospitalized on a metabolic service. All had been standardized on insulin in one form or another before each case was transferred to a single dose of NPH insulin before breakfast. It was found that the postprandial effects of NPH insulin were superior in all cases that had previously received only protamine zinc insulin and were as good in almost all cases previously receiving protamine zinc insulin and unmodified insulin.

Sharkey and King[19] reported an experience gained from 18 months' observation of 28 diabetic patients both in the hospital and in office practice. Sixteen cases were treated satisfactorily with NPH insulin alone, and the remaining 12 required NPH insulin and unmodified insulin in a mixture. Insulin reactions were reduced in severity and over-all control was improved.

Edwards, Vance, and Mulholland[20] made comparisons of 2:1 mixture, NPH insulin and globin insulin with zinc in 21 cases. Their findings bore out the observation that all three modifications can be used satisfactorily in the mild and moderate diabetic, but in the more severe or complicated case the "carry-over" effect of NPH insulin or the 2:1 mixture was found to be highly desirable.

Dolger[21] described a broad experience covering 185 severe diabetic patients observed for extended periods. Seventy-two of his group were satisfactorily controlled with NPH insulin alone. The remainder required mixtures in varying proportions. The author commented that NPH insulin will provide adequate coverage for 40 per cent of the patients with severe diabetes mellitus and is also suitable for patients whose insulin requirements are low or moderate.

Groff, Engelhardt, and Skelton[22] studied 17 hospitalized diabetic patients who had been selected because their cases were moderately severe or severe, and they were free of discernible complicating factors. They found the improvement in control of diabetes in this group to be particularly valuable and noted remarkably uniform activity of the preparation during the 24 hours.

Greenhouse,[23] drawing on four years' experience with various modifications of insulin, pointed out that NPH insulin has other advantages over and above improved timing characteristics. Insulin reactions tend to be less insidious than those resulting from protamine zinc insulin and, therefore, easier to recognize and treat. Furthermore, local allergic reactions tend to be diminished when NPH insulin is used. Palmer and others[24] also reported a lowered incidence of insulin reactions in 28 patients observed over a two-year period.

Swallow and Chute[25] obtained as good or better control with a single injection of NPH insulin as obtained with double injection of unmodified insulin and protamine zinc insulin in 10 out of 18 children. Two of the cases, both under 6 years, were noteworthy in that daytime hyperglycemia was associated with nocturnal hypoglycemia.

Shuman and Francis[26] indicated that NPH insulin was effective in controlling both the fasting and the postprandial glucose levels in the majority of 33 patients studied, despite both medical and surgical complications.

Other published reports[27-31] mention the utility of NPH insulin in a wide spectrum of the diabetic population resulting in satisfactory control with a minimum of inconvenience to the patient.

EXPANDED CLINICAL TRIAL

There are several phases involved in the investigation of any new therapeutic agent which have been successively undertaken in studies of NPH insulin. After determination of its time activity in intensive but small-scale comparisons, the new preparation was applied on a larger scale in hospital wards and in outpatient groups. As a final step, when supplies became available, experimentation was extended and more and more investigators began to test the preparation under conditions of actual wide-scale practice until several thousand cases were under treatment. Reports of this experience were accumulated; 1,281 cases were in sufficient detail to permit analysis. It was anticipated that this study would be heavily weighted with problem cases not previously controlled satisfactorily. As shown in Figure 1, such proved to be the case. Of the 1,281 cases, 522 were classified as severe, brittle, or juvenile, 562 as moderate, and only 197 as mild. Furthermore, in age distribution, one third of the group was under 30 years of age (Figure 2). Practically all patients in these studies were diabetics whose "pedigrees" were well known to the investigators, and it can be assumed that the therapy used prior to NPH insulin controlled the disease as well as possible and had shown the best results in each case.

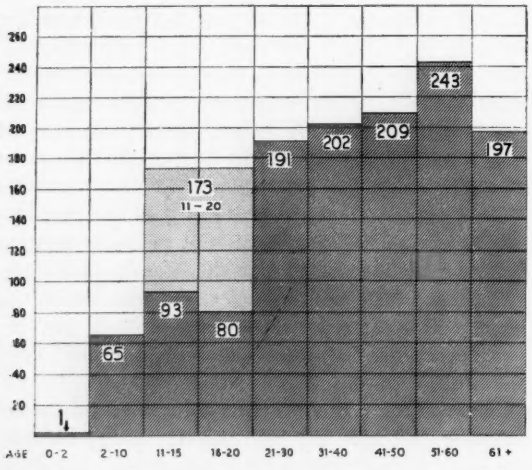

FIGURE 2 Age distribution of 1,281 cases. Total numbers of patients in each age group are indicated

The types of insulin therapy before NPH insulin was utilized are shown in Figure 3. Of all patients, 89.5 per cent were taking protamine zinc insulin in one form or another, with the insulin mixtures accounting for almost one-half of the entire group.

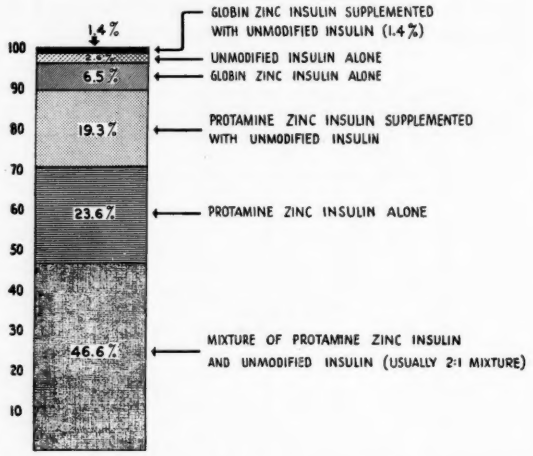

FIGURE 3 Types of insulin therapy utilized prior to NPH insulin study

Of much interest are the data relative to the degree of diabetic control achieved in the comparative study (Figure 4). In all three groups classified mild, moderate, or severe there was a significant shift toward better management when NPH insulin was used. This shift applied not only to the severe group, where it was anticipated that more efficient timing of insulin effect would result in improvement, but also most markedly to the mild group where Izzo has shown that timing characteristics of insulin are least critical.[7] In the mild group, "excellent" control was obtained in 39 per cent of the cases on prior insulin therapy, and this figure rose to 65 per cent following treatment with NPH insulin. Cases previously classified as having "poor" control diminished to 1.7 per cent.

Results in the "severe" group, both before and after NPH insulin, tend to emphasize the limitations of any insulin preparation used, since obviously no one insulin preparation as yet available is capable of controlling satisfactorily all cases of diabetes. Nevertheless, the data do show that improved control resulted when NPH insulin was used. Stephens, Donaldson, and Marble[32] have shown that the employment of supplements of unmodified insulin, either as separate injections or mixed with NPH insulin, provides better results, particularly in the juvenile patients. The possibility of employing such

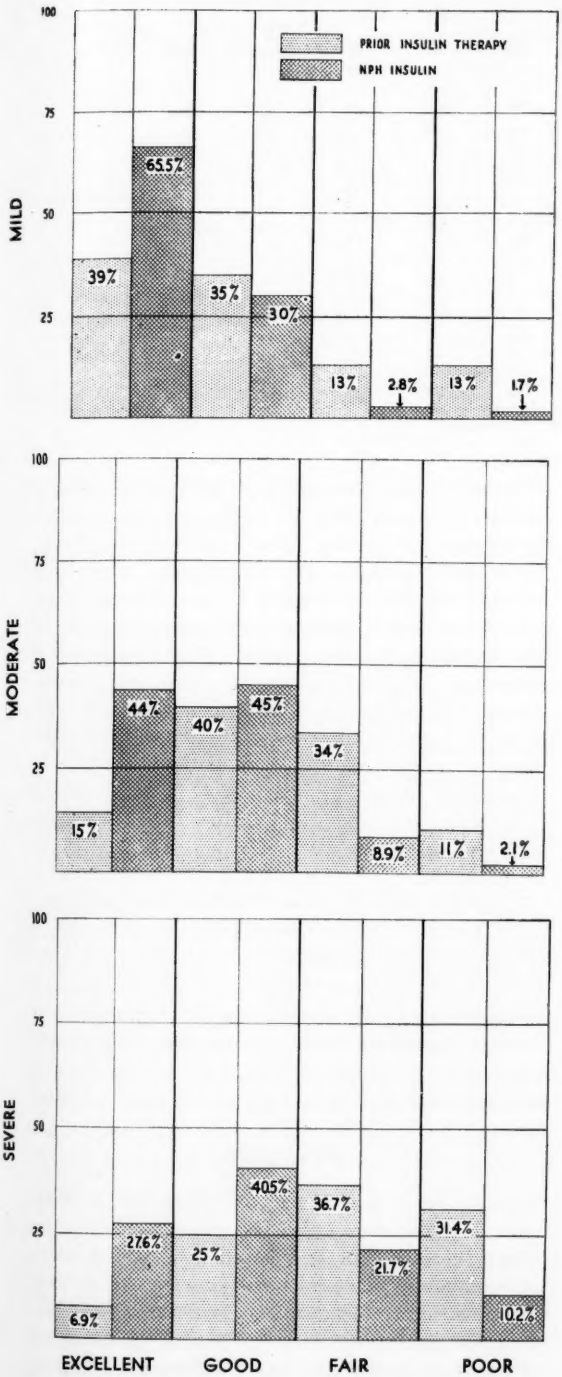

FIGURE 4 Degree of control. Note that the control tends to shift towards improvement in each group

a mixture had been previously suggested by Sprague,[33] and by Shuman and Francis.[26]

The incidence of insulin reactions was also of interest, and investigators were asked to enumerate the number and time of occurrence of reactions in the cases they observed. Over one-half reported a lessening in number of reactions, and an additional 23 per cent indicated that there had been no reactions at all when NPH insulin was used (Figure 5).

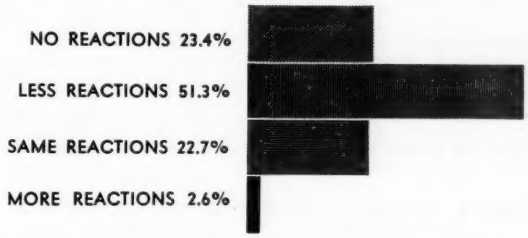

FIGURE 5 Reactions with NPH as compared with other insulins (based on groups reported, not individual cases)

There was a lack of uniformity as to time of day that reactions were observed. This is surprising, since protamine zinc insulin is more prone to cause reactions in the early morning hours and globin insulin with zinc has a tendency to exhibit its peak effect manifested by hypoglycemia in the middle to late afternoon hours. Of those patients who had reactions while using NPH insulin, 34.5 per cent experienced them in the morning, 37.7 per cent reported afternoon reactions, and 27.8 per cent had them in the evening. These figures seem to indicate that hypoglycemic reactions with NPH insulin follow individual variations in the patient's response to insulin, modified by diet and exercise. A similar lack of pattern in time of hypoglycemia was noted by Peck and Kirtley[6] at Indianapolis General Hospital.

CLINICAL EXPERIENCE OUTSIDE THE UNITED STATES

Outside the United States, a number of investigators have also studied NPH insulin.[34-54] The majority of the published reports, mostly from Latin America, are summarized in Table 1. Of the 17 groups tabulated, comprising 240 patients from 10 different countries, approximately 39 per cent were classified as severe, brittle, or juvenile, 46 per cent as moderate, and only 15 per cent as mild. As for previous treatment, 24 per cent were using protamine zinc insulin alone, 47.5 per cent mixtures of unmodified and protamine zinc insulin (mostly 2:1), 5 per cent unmodified alone, 5 per cent

TABLE 1 SUMMARY OF SEVENTEEN GROUPS OF PATIENTS

Investigator	No. Patients	Ages	Severity			Previous Insulin				
			Sev.	Mod.	Mild	PZI	2:1	Unmod.	Globin	Other
Arduino, Brazil	13	20-60	3	10	—	3	10	—	—	—
Bermudez, Mexico	10	40-80	—	10	—	10	—	—	—	—
Cardonnet, Argentina	39	5-75	23	11	5	10	19	2	5	1
Cervino, Uruguay	6	10-60	5	1	—	—	3†	1	—	2
Chanis, Panama	7	?	—	7	—	—	—	7	—	—
Houssay, Argentina	10	5-63	4	6	—	7	3†	—	—	—
Jauregui, Mexico	12	20-75	2	6	4	7	3	—	—	—
Linder, S. Africa	11	?	2	5	4	2	2	—	6	1
Montagna, Argentina	7	5-15	7	—	—	—	7	—	—	—
Osio, Paraguay	34	10-75	4	14	16	3	10	—	—	21
Paniagua, P. Rico	22	5-80	22	—	—	6	12	—	2	— *
Richer, Paraguay	7	15-75	1	1	5	—	7	—	—	—
Rocca, Uruguay	12	15-70	5	6	1	3	6	2	1	—
Saldun, Uruguay	15	5-60	15	—	—	—	15†	—	—	—
Schneider, S. Africa	14	?	—	14	—	7	7	—	—	—
Zazaleta, Mexico	10	40-80	—	10	—	—	10	—	—	—
Pulver, Switzerland	11	?	?	11	?	—	—	—	—	11‡
TOTALS	240		93	112	35	58	114	12	14	36

* Two new patients in each group. † Also 1:1, 3:1, and other mixtures. ‡ "Di-Insulin."

TABLE 2 INSULINS: PERCENTAGE OF USE IN FOUR COUNTRIES

Country	Type of Insulin	Year (Per Cent) 1946	1948	1950
Argentina	Unmodified	50	50	50
	Modified	50	50	50
Brazil	Unmodified	60	60	50
	Modified	40	40	50
Mexico	Unmodified	45	45	35
	Modified	55	55	65
United States	Unmodified	35	30	30
	Modified	65	70	70

globin, 5 per cent "Di-Insulin," and 11 per cent a variety of insulin regimens. Six patients (2.5 per cent) were new diabetics.

It is noteworthy, however, that protamine zinc insulin was never as widely adopted in some countries as in the United States, as shown in Table 2. Although a poor appreciation of the clinical attributes of the long-acting insulins has been held partially responsible, another interesting possibility must be considered, namely that the rate of action of protamine zinc insulin might not be well adapted to the dietary habits of the patients in countries where the "continental" breakfast is the rule and the preponderance of daily caloric intake is from 1 to 8 p.m. The 2:1 mixture of unmodified insulin and protamine zinc insulin has actually been used only to a minor extent in Latin America. Table 1 is misleading in this respect, because the authors mentioned do not represent average practice but are leaders in the field of diabetes in their respective countries.

Because of its more ideal rate of onset and duration of action, it was theorized that NPH insulin should facilitate the management of diabetes in countries where the type of diet described above is customary. As a rule, in the studies conducted abroad, distribution of the diet and the mealtimes were made to conform to local habits, only the total caloric intake and the carbohydrate, protein, and fat content being controlled. The impossibility of compelling the diabetic patient to change the habitual mealtimes prevalent in his country is obvious when customs and working hours with their economic implications are considered. The diets outlined in Table 3, satisfactorily adopted by investigators in Brazil, Argentina, Mexico, and suggested by Constam[55] in Switzerland, are worth comparing with the typical diet used in the United States.

In the 240 patients observed for periods of time ranging from 30 to 120 days, NPH insulin afforded a degree of control which paralleled the observations made in the United States. It is of interest to record that results observed with the diet distributions summarized in Table 3 were extremely satisfactory, for they indicate the perfect adaptability of this new modified insulin to types of diet found in Latin America and in some European countries.

DISCUSSION

There has been a gradual evolution of methods of insulin therapy in the management of diabetes over the last quarter century. The original short-acting insulin requiring multiple daily injections ceased to be the sheet anchor of management with the introduction of protamine zinc insulin, which rapidly became the foundation of treatment, embellished with supplementary doses of unmodified insulin. Clinical experience dictated the next

TABLE 3 DIET DISTRIBUTION AND MEALTIME IN FIVE COUNTRIES

	Breakfast	Mid Morning Meal	Lunch	Mid Afternoon Meal	Dinner	Bedtime Meal
	(Figures are percentages of total daily diet)					
Arduino-V. da Silva Brazil	20 7 a.m.	——	30 Noon	10 3-4 p.m.	30 7-8 p.m.	10 10-11 p.m.
Bermudez-Zabaleta Mexico	25 8:30 a.m.	——	50 1:30 p.m.	——	25 8:30 p.m.	——
Cardonnet-Staffieri Argentina	15 8 a.m.	——	35 1 p.m.	15 3-4 p.m.	35 8 p.m.	——
Constam Switzerland	20 7-8 a.m.	6 10 a.m.	27 12-12:30 p.m.	20 4 p.m.	27 6-7:30 p.m.	——
United States	20 7 a.m.	——	40 Noon	——	40 6:30 p.m.	——

step, via a time-consuming series of comparisons of preparations having all sorts of intermediate timing effects, which led to the conclusion that a preparation having the action characteristics of a 2:1 (protamine zinc insulin: insulin) mixture exerted the most desirable effects for most patients. Then followed a deliberate attempt to produce a preparation, stable and uniform, which could duplicate this action in a practical manner. That this preparation was one that could be prepared in crystalline, highly purified form was undoubtedly fortuitous —NPH insulin crystals happened to exert the desired time action. There is but limited opportunity to change this rate of action except by the addition of required amounts of unmodified insulin to the injection in order to provide a more intense daytime effectiveness.

For the majority of patients the timing of NPH insulin represents the most satisfactory action as measured by minimum number of injections, satisfactory overlap (nocturnal effect), and relative freedom from hypoglycemia. Even in the severe unstable cases some improvement can be anticipated. But it is not a panacea, and it does not change the severe unstable case to a stable one. Such exceptional cases remain difficult individual problems even though management of the bulk of cases is simplified and improved.

SUMMARY

The development of modified insulin preparations is briefly summarized and the literature reviewed. Results obtained in a group of 1,281 cases in a general clinical trial of NPH insulin are described. An additional summarization of experience on 240 cases collected from studies outside the United States is presented. These data bear out the conclusion that NPH insulin exhibits the most generally useful time action available to date.

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Amputation of the Lower Extremity in Diabetes Mellitus

A FOLLOW-UP STUDY OF 294 CASES

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The duration of life in patients with diabetes mellitus who have required an amputation of a lower extremity because of gangrene generally is regarded as relatively short. However, the available statistical information on the life expectancy of such patients is meagre. Joslin stated that "Among 206 gangrene cases, 48 died in the first year after operation, but the average length of life was 2.9 years after operation."[1] In my experience reported in 1948[2] about 40 per cent of diabetic patients were found at that time to live more than three years after amputation of a leg.

Additional information also is needed with reference to the number of patients who require amputation of the remaining leg, and the length of the interval between amputations. Joslin[3] stated that "Of 100 patients, 39 subsequently required amputation of the second leg," but the length of the period between amputations was not given. In my study mentioned above, it was observed that about 40 per cent of diabetic patients who survive for three years after the loss of one leg will have required amputation of the second leg within that period.

The present study, based on a larger series of cases and including many in which amputations were performed within the past decade, was undertaken to determine the postoperative course at the present time. Many factors, such as prolongation of life in the general population, the use of new antibiotic preparations, and better understanding of the problems of peripheral vascular disease, might be reflected in a longer survival period following amputation and a decrease in the number of second amputations.

CLINICAL MATERIAL

This study deals with 294 cases of diabetes mellitus from the private practice of the author in which there were

TABLE 1 Age at time of amputation in 294 cases of diabetes

	30-39	40-49	50-59	60-69	70-79	80-89	Total
Male	2	12	55	63	34	—	166
Female	1	4	28	63	29	3	128
Total	3	16	83	126	63	3	294

TABLE 2 Survival period between amputation and death in 172 cases of diabetes

Years	Male Midleg	Male Midthigh	Female Midleg	Female Midthigh	Total
Less than 1	9	5	11	7	32
Between 1 and 2	11	5	12	2	30
Over 2 and under 3	4	5	5	7	21
Over 3 and under 4	12	4	4	3	23
Over 4	2	10	3	3	18
Over 5	3	3	1	3	10
Over 6	1	4	3	3	11
Over 7	4	2	4	1	11
Over 8	1	3	—	—	4
Over 9	—	3	—	1	4
Over 10	3	4	1	—	8
Total	50	48	44	30	172

TABLE 4 Survival period after amputation in cases of diabetes with age over 60

Survival Period	3 Years Male	3 Years Female	3 Years Total	5 Years Male	5 Years Female	5 Years Total
Living patients who survived for period shown	19	17	36	9	10	19
Dead patients who survived for period shown	31	25	56	14	14	28
Patients who died within period shown	29	31	60	46	42	88
Total patients followed sufficient time	79	73	152	69	66	135

3-year period
92 of 152 or 60 per cent survived
Males: 50 of 79 or 63 per cent survived
Females: 42 of 73 or 58 per cent survived
5-year period
47 of 135 or 35 per cent survived
Males: 23 of 69 or 33 per cent survived
Females: 24 of 66 or 36 per cent survived

one or more amputations of a lower extremity. Of these patients, 166 were male and 128 female. The distribution by age and sex is shown in Table 1.

Of the 294 cases, 172 were followed until the time of death. The period of survival of this group is summarized in Table 2. Of the 122 patients who are still alive, 57 have survived operation for less than 3 years and 65 for longer than 3 years. Amputation of the second leg has been required by 72 of the 294 patients. In 52 of these patients, the second amputation was performed within three years of the first amputation. The remaining 20 patients required a second operation more than three years after the first amputation.

These data show that of 237 patients who were followed to the time of death or for a period of three years, 154 or 65 per cent survived at least 3 years after amputation of the first leg. Of the 209 patients who were followed to the time of death or for a period of five years, 85 or 41 per cent survived for five years or longer (Table 3). These findings show a longer life expectancy than that found in the previous study.[2]

A comparison of the period of survival of males and females suggests a longer period of survival in the males. Further analysis shows that the sex difference is more apparent than real and was caused by the inclusion of a greater number of males of the younger age groups (Table 1). This disparity disappears when the groups are limited to patients over 60 years of age (Table 4).

It is a melancholy fact that many patients who have lost one leg are later obliged to lose the remaining leg as well. In this series, 172 patients were followed long enough to determine the frequency of second amputations in the three-year period following the first operation, and 122 long enough to evaluate a five-year period. Thirty per cent of these patients required a second amputation within three years and 51 per cent within

TABLE 3 Survival period after amputation in cases of diabetes

	3 Years Male Thigh	3 Years Male Leg	3 Years Male Total	3 Years Female Thigh	3 Years Female Leg	3 Years Female Total	3 Years Grand Total	5 Years Male Thigh	5 Years Male Leg	5 Years Male Total	5 Years Female Thigh	5 Years Female Leg	5 Years Female Total	5 Years Grand Total
Living patients who survived for period shown	25	16	41	7	17	24	65	14	9	23	4	10	14	37
Dead patients who survived for period shown	33	26	59	14	16	30	89	19	12	31	8	9	17	48
Patients who died within period shown	15	24	39	16	28	44	83	29	38	67	22	35	57	124
Total patients followed sufficient time	73	66	139	37	61	98	237	62	59	121	34	54	88	209

3-year period
154 of 237 or 65 per cent survived
Males: 100 of 139 or 72 per cent survived
Females: 54 of 98 or 55 per cent survived

5-year period
85 of 209 or 41 per cent survived
Males: 54 of 121 or 45 per cent survived
Females: 31 of 88 or 35 per cent survived

five years (Table 5). Although the incidence of second operations is high, a comparison with the incidence reported in 1948[2] suggests a favorable trend.

TABLE 5 Frequency of amputation of second extremity in cases of diabetes

	Period After First Amputation	
	3 Years	5 Years
Second amputation required within period shown	52	62
Second amputation required after period shown	20	10
Patients who survived without second amputation more than period shown	100	50
Total patients followed sufficient time	172	122

52 of 172 or 30 per cent required second amputation within 3 years
62 of 122 or 51 per cent required second amuptation within 5 years

COMMENT

Reliable information on the natural course of the disease is necessary in order to evaluate the efficacy of therapeutic procedures. It is hoped that the present study will contribute to knowledge of the life expectancy of patients with diabetes mellitus who require amputation of the lower extremity because of gangrene. Furthermore, it is important to have available information concerning the expected incidence of second amputations and the predicted intervals between amputations. With such information available, patients who have undergone an amputation of one leg serve, to a certain extent, as controls in the evaluation of various therapeutic procedures, such as the use of sympathectomy, vasodilator drugs and lipotropic agents.

SUMMARY

This paper presents a study of the life expectancy in a series of 294 cases with diabetes mellitus who have required amputations of one or both lower extremities because of gangrene. Sixty-five per cent survived more than three years after amputation of the first leg, and 41 per cent survived five years or longer. There were no significant sex differences in the survival period.

One hundred and seventy-two patients who suffered an amputation of one leg were followed long enough to determine the incidence of second leg amputation. Of these, 30 per cent required amputation of the remaining leg within a period of three years, and 51 per cent required the second amputation within five years.

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ABSTRACTS

ANONYMOUS. Keep extra insulin, syringe on person for atom emergency, diabetics warned. Am. Druggist *125*:29-31, March 3, 1952.

To be prepared for an atomic bomb attack, every diabetic taking insulin should at all times have on his person an extra bottle of insulin plus an extra syringe with 2 needles. This precaution is suggested by the American Diabetes Association. In addition, the Association recommends that in the event of an atomic attack, a diabetic should use his oldest supply of insulin first, test his urine regularly, eat too little rather than too much, carry a diabetic identification card, prepare to take complete care of himself if he remains uninjured, and teach his friends and family to take care of his diabetic needs in the event of an emergency.

BANERJEE, SACHCHIDANANDA; DEB, CHANDICHARAN; AND BELAVADY, BHAVANI *(Dept. of Physiology, Presidency Coll., Calcutta):* Effect of scurvy on glutathione and dehydroascorbic acid in guinea pig tissues. J. Biol. Chem. *195*:271-76, March 1952.

The glutathione content of blood and the glutathione and dehydroascorbic acid content of adrenals, pancreas, spleen, liver, kidneys, and small intestine were determined in scorbutic and pair-fed normal guinea pigs. Glutathione was found to be significantly diminished in blood, adrenals, pancreas, and spleen; in other tissues studied, the value was not changed significantly. The lowering of the glutathione value in the pancreas of scorbutic guinea pigs was maximal. Dehydroascorbic acid was absent in the tissues of normal guinea pigs, but it was present in considerable amounts in the tissues of scorbutic guinea pigs.

The authors suggest that the diminished insulin secretion in scorbutic guinea pigs, which they previously reported, may be due to the combined effect of diminished glutathione content and increased dehydroascorbic acid content of tissues in general and of pancreas in particular.

BARACH, JOSEPH *H. (Pittsburgh):* Modern concepts of the physiopathology of diabetes mellitus. Am. J. Digest. Dis. *19*:61-64, March 1952.

All considered, the available facts at this stage in our knowledge of diabetes, both experimental and clinical, point clearly to hormonal imbalance of the pancreas, pituitary, adrenals, and thyroid. Whatever alters the smooth and normal functioning of the pancreatic hormone disturbs sugar production and sugar utilization primarily and protein and fat metabolism secondarily at the various intermediary stages. Whatever the resulting nutritional disturbances may be, they are fortunately corrected, in a large measure, by the administration of insulin. This we see from day to day.

It is true that certain fundamental questions still have to be answered, particularly those pertaining to intermediate metabolism; however, increasing knowledge concerning the hexokinase reaction, phosphorylation, and the part played by pyruvic acid seems to be leading us in the direction of a more complete understanding of this disease.

BEDELL, ARTHUR J. (*Albany Med. Col., Albany, N. Y.*): The intraocular signs of diabetes. M. Rec. & Ann. *36*:898-99, March 1952.

A series of color photographs taken at 3 to 6-month intervals over a period of years made it possible to note retinal changes in the diabetic. As retinopathy increases, the most striking alterations are in the retinal veins: an irregular increase in size and frequently also in length. The vein is uneven in caliber, and as it lengthens it frequently forms loops or even bow knots. As the disease progresses and time passes, the veins tend to break, so that there are numerous hemorrhages—some small, discrete or perivascular; others large, between the vitreous and retina; and some so great that the entire fundus is obscured. When the extravasations become organized, retinitis proliferans develops, starting most often on the disk and extending from it along the major veins. With fresh hemorrhages the new vessels increase in number and size, and very large, thick, elevated vascularized membranes are formed. Where areas of exudate are visible and not uncommonly beneath the translucent retina, deeper exudates are also seen. When the retinitis proliferans is thin and the vessel changes are slight, it is possible to have a recession when the fundus returns to normal. If, however, connective tissue has formed and great proliferans sheets have developed, there is no hope of such a favorable outcome and no regression will take place.

BEIDLEMAN, BARKLEY; AND DUNCAN, GARFIELD, G. *The Benjamin Franklin Clin., Pennsylvania Hosp. and Jefferson Med. Coll., Philadelphia):* Charcot joints and infectious vascular lesions of bones in diabetes mellitus. Am. J. Med. *12*:43-52, January 1952.

The authors describe two types of destructive lesions of the bones of the foot, demonstrable by roentgen ray examination, in patients with diabetes mellitus. The first type attributable to diabetic neuropathy, is characterized by gradual dissolution of the tarsal bones and their articulations (the Charcot joint); the second type is characterized by rarefaction of the phalanges and metatarsals secondary to chronic infection in the adjacent soft tissues and arterial insufficiency. Four cases illustrative of Charcot joint in diabetes mellitus are reported, two of them showing, in addition, the second type of bony lesion.

BELTRAN BIGORRA, F.; VIGUERA LOBO, J. M.; CASABUENA PUIG, A.; AND PRIMO YUFERA, E. (*Spain*): Hypoglycemic action in centaurea. Farmacognosia *10*:197-216, 1950 [Abstr. from Chem. Abstr. *45*:2582, March 25, 1951].

When the aqueous extracts of some species of centaurea are injected intravenously into rabbits, they cause a mild and variable drop in blood sugar.

BERGER, HERBERT *(U.S. Public Health Hosp. and Med. Serv. of Berger Clin., Richmond Mem. Hosp., Staten Island, N. Y.):* Method of increasing sensitivity of glucose tolerance test. J.A.M.A. *148*:364-66, February 2, 1952.

The administration of 100 mg. of corticotropin prior to a standaırd glucose tolerance test increased the blood sugar levels of a group of siblings of known diabetics, as well as those of the diabetics themselves. Except in two instances, the corticotropin did not affect the curves of normal persons without a family history of diabetes. The author suggests that corticotropin administered before a standard glucose tolerance test may reveal potential diabetics not discoverable by other means.

BIDMEAD, D. S.; AND WATSON, D. *(South-west and Oxford Regions, Rheumatism Res. Unit, Royal National Hosp. for Rheumatic Dis., Bath):* The determination of blood glutathione by amperometric titration. J. Clin. Path. *5*:30-35, February 1952.

A simple and rapid technique is described for the determination of blood glutathione. Results are given for recoveries of glutathione added to blood of known sulphydryl content and for the estimation of blood nonprotein sulphydryl compounds carried out in parallel by iodometric and nitroprusside methods and by a silver nitrate titration. Titration with Ag ions to an amperometrically found end point is shown to provide a more accurate, specific, and reliable method for the determination of reduced glutathione in blood.

BLACK, K. O.; MACDONALD, I.; REID, E.; AND YOUNG, F. G. *(Dept. of Biochemistry, Univ. Coll., London):* Trial of pituitary growth hormone in a case of hyperinsulinism due to islet-cell adenoma. Lancet *1*:19-21, January 5, 1952.

Two trials of growth hormone therapy were given to a patient with hyperinsulinism whose symptoms had not yet been relieved by partial pancreatectomy. After the growth hormone trial, a second operation disclosed an islet-cell tumor imbedded in the head of the pancreas. The observed effects of growth hormone were as follows: a substantial reduction in the carbohydrate intake required to prevent hypoglycemia (first trial); a slight over-all rise in the blood sugar level (first trial, 60 mg. dose) or a well-marked but transient rise when glucose supplements were standardized (second trial, 100-mg. dose); a slight pyrexial reaction but no local reaction (second trial); and loss of weight in spite of increased caloric intake. Growth hormone had a negligible short-term effect on the blood sugar level, as shown by its failure to relieve an attack of hypoglycemia. A brief discussion compares these results with experiments in animals.

BLANDI, MICHELE *(Cosenza, Italy):* Allergy to insulin: Report of a case. Rassegna med. *28*:219, December 1951.

The author reports severe allergic symptoms ensuing ½ hour following 10 units of unmodified insulin used to study the glycemic profile of a patient. The reaction, characterized by erythema and pruritus, started at the site of injection, progressing to the arm and neck. It was followed by edema of the tongue and glottis, and cyanosis. Under calcium and other therapeutic agents, the patient recovered.

BORNSTEIN, J.; AND LAWRENCE, R. D. *(Biochemical and Diabetic Depts., King's Coll. Hosp., London):* Plasma insulin in human diabetes mellitus. Brit. M. J. *2*:1541-44, December 29, 1951.

An assay method in which rats are made alloxan-diabetic, are hypophysectomized and adrenalectomized, and are subsequently markedly sensitive to extremely small amounts of insulin was used in analyses of plasma insulin of diabetic patients. From these analyses of plasma insulin in clinical cases, it is considered that two main types of human diabetes exist and can be distinguished. The first is severe and is characterized by weight loss and ketosis as well as hyperglycemia; it occurs in any age group, but mainly in the young. Their plasma contains no available insulin but renders the rats insensitive to subsequent insulin injections. Such patients require insulin treatment in order to live. The second type consists mainly of middle-aged obese diabetics, females being more numerous, and is distinguished by the absence of ketosis and loss of weight. The plasma of these individuals contains available insulin (roughly 70 per cent of normal controls) but does not make rats insensitive to insulin. Their diabetic state is easily controlled by diet alone, especially when obesity is thereby reduced.

BORNSTEIN, J.; MEADE, B. W.; AND SMITH, M. J. H. *(King's Coll. Hosp. Med. Sch., Denmark Hill, London):* Salicylates and carbohydrate metabolism. Nature, London *169*:115-16, January 19, 1952.

A number of workers have reported that the administration of salicylates prevents diabetic glycosuria in man, and Ingle has shown that aspirin reduces the glycosuria of rats made mildly diabetic by means of partial pancreatectomy. The effect of salicylates on the blood glucose of fasting alloxan-diabetic rats was investigated in two groups of animals, one group of rats having been given salicylates at 0 hour. The results show that there was no important difference between the two groups at the start of the experiment but that a significant fall in blood glucose occurred in alloxan-diabetic animals treated with salicylate. This fall was significantly different from any deviations observed in the control of diabetic animals.

BOUCOT, KATHARINE R.; DILLON, EDWARD S.; COOPER, DAVID A.; MEIER, PAUL; AND RICHARDSON, RUSSELL *(Philadelphia):* Tuberculosis among diabetics: The Philadelphia survey. Am. Rev. Tuberc. *65*:1-50, January 1952.

The project was launched as a co-operative undertaking of the Philadelphia County Medical Society and the Philadelphia Tuberculosis and Health Association, with a committee of fourteen experts in charge of the three fields involved: diabetes, tuberculosis, and radiology. The study was begun in December 1945, and was completed in Rebruary 1947. One mobile and one stationary photofluorographic unit were used. Diabetics and nondiabetics were examined intermittently at both units so that physicians interpreting the films were never aware of whether or not particular films had been taken on diabetics or on nondiabetics. The criteria for the diagnosis of diabetes were those commonly used by workers in this field: a fasting blood sugar of 130 or a blood sugar at any other time of 170, usually with glycosuria. Almost all of these patients had a diagnostic blood sugar of 200 or more.

The prevalence of tuberculosis was 8.4 per cent among 3,106 Philadelphia diabetics surveyed in 1946. This was twice as high as the prevalence in a group of apparently healthy industrial workers adjusted for age, race, and sex. The diabetics younger than forty had a prevalence of active tuberculosis of 5.3 per cent, as contrasted with 1.7 per cent for those older than forty. The diabetics younger than forty had a tuberculosis prevalence of 5 per cent with diabetes of less than ten years' duration, whereas the tuberculosis prevalence was 17 per cent when the diabetes had been present for more than ten years. This relationship was not noted in persons older than forty. The situation was similar when active tuberculosis only was considered. The prevalence of active tuberculosis increased from approximately 1.5 per cent for those who received no insulin or no more than 40 units to 5.3 per cent for those who received more than 40 units each day.

BROWN, E. M., JR.; LUKENS, F. D. W.; ELKINTON, J. R.; AND DEMOOR, P. *(Univ. of Pennsylvania, Philadelphia):* Observations on the metabolic and antiarthritic effects of ACTH and cortisone in diabetics. J. Clin. Endocrinol. *10*:1363-74, November 1950.

These observations, which supplement the studies of others in nondiabetics, suggest that the effect of the adrenal hormones in rheumatoid arthritis is not closely correlated with the gross manifestations of their metabolic functions and therefore may be independent of these activities.

BROWNING, HENRY; AND RESNIK, PHILIP *(Yale Univ. Sch. of Med., New Haven, Conn.):* Homologous and heterologous transplantation of pancreatic tissue in normal and diabetic mice. Yale J. Biol. & Med. *24*:141-52, November 1951.

Differentiated islet tissue appeared in the pancreas of the developing mouse between birth and the third day of postnatal life. Embryonic and newborn pancreas, when transplanted intraocularly into animals of the same strain, showed differentiation of islets, but acini were represented only by occasional cysts. The transplants persisted indefinitely. Growth, in the sense of actual increase in size, was frequent only in embryonic transplants. Adult pancreas, similarly transplanted, usually showed persistence without change.

Similar transplants of embryonic and newborn pancreas to animals of a different inbred strain showed similar differentiation. Growth, even of embryonic pancreas, was rare. Both tissues regressed after the first three weeks of intraocular life. Adult pancreas began to be absorbed from the time of transfer. Intraocular and subcutaneous transplants of embryonic and newborn pancreas into alloxan-diabetic mice of the same strain showed differentiation and growth similar to those seen in intraocular transplantation in untreated hosts. Transplants of embryonic pancreas placed beneath the capsule of the spleen failed to survive.

Intraocular or subcutaneous transplants of one or two embryonic or newborn pancreases had no effect on the course of the glycosuria in the majority of alloxanized hosts. Subcutaneous transplantation of four newborn pancreases gave reduction of glycosuria and an apparently indefinite survival in 66 per cent of hosts.

BRYANT, KATHLEEN; MARTIN, CONSTANCE; SCHUMACHER, MARY T.; DAUM, KATE; AND TUTTLE, W. W. *(Depts. of Physiology and Nutrition, Coll. of Med., State Univ. of Iowa, Iowa City):* Effect of aging and various types of breakfasts on the blood sugar level. J. Am. Dietet. A. *28*:17-22, January 1952.

On the basis of data collected from one group of men ranging in age from 20 to 30 years and another group from 60 to 84 years relative to the blood sugar response following different types of breakfasts, the following conclusions are drawn: The blood sugar level following breakfast is significantly affected by the amount of protein in the meal. In this experiment 10 gm. were not sufficient to maintain the level 3½ hours after the breakfast at, or above, the fasting level. Twenty-five gm. protein were found to be adequate in this respect. The effects of the protein in the breakfast on the blood sugar level following the meal were the same regardless of whether it was of plant or of animal origin. Both the younger and the aged group experienced the same blood sugar changes following similar breakfasts.

BUNIM, JOSEPH J.; KALTMAN, ALFRED J.; AND MCEWEN, CURRIER *(Dept. of Med. and the Study Group on Rheumatic Diseases of New York Univ. Coll. of Med., and the Children's Med. Serv. of Bellevue Hosp., New York City):* Diabetogenic effect of cortisone and ACTH in a non-diabetic patient with rheumatoid arthritis. Am. J. Med. *12*:125-34, January 1952.

A report is given of the diabetogenic effect of cortisone and ACTH administered intermittently over a period of

one year to a girl of 10 years with severe rheumatoid arthritis who was nondiabetic and had no family history of diabetes. Marked improvement in the arthritis occurred when adrenocortical hormones were given, and relapse followed their withdrawal. Glycosuria, relatively mild hyperglycemia, and abnormal glucose tolerance were consistently associated with the daily administration of 60 mg. or more of cortisone and 20 mg. of ACTH but disappeared when these agents were discontinued. The glycosuria responded to insulin but was not affected by DCA or BAL. The disturbance in carbohydrate metabolism did not interfere with the therapeutic efficacy of cortisone or ACTH.

CARDONNET, LUIS J.; AND STAFFIERI, JUAN J. *(Rosario, Argentina)*: Trial with modified NPH insulin. Prensa méd. argent. 39:47-69, January 11, 1952.

Thirty-nine diabetics previously treated with several insulin regimens—including unmodified insulin, protamine zinc insulin, globin insulin and different mixtures—were transferred to NPH insulin. As for degree of severity, 23 were classified as brittle or severe, 11 as moderate, and 5 as mild. Two had not used insulin previously. The results were extremely favorable with the new modified insulin; the authors considered it the type of insulin with the widest therapeutic range. Following the eating habits prevalent in Argentina, the diet distribution was as follows: breakfast, 5 per cent of total daily caloric intake (8:00 a.m.); lunch, 35 per cent (1:00 p.m.); midafternoon meal (the classic *merienda*), 15 per cent (3:00 to 4:00 p.m.); and dinner, 35 per cent (8:00 p.m. or later). NPH insulin was found to be perfectly adapted to these eating habits, and no supplementary feedings were required.

CARR, JOHN H.; KEMPE, C. HENRY; SILVER, HENRY K.; SMYTH, FRANCIS SCOTT; GOFMAN, JOHN W.; AND JONES, HARDIN B. *(Div. of Pediatrics, Univ. of California Sch. of Med., San Francisco, and the Donner Lab., Berkeley)*: The lipoproteins of serum in infancy and childhood. II. Lipoprotein levels in juvenile diabetes mellitus. J. Pediat. 40:19-23, January 1952.

Determinations of the concentrations of certain lipoprotein molecules (Sf 10-20 class) are reported for 46 cases of juvenile diabetes mellitus. Diabetic girls and diabetic boys have higher levels than their normal counterparts. The values for the girls were higher than those for boys. No close correlation was found in this age group between the level of Sf 10-20 lipoprotein molecules in the serums and (1) the duration of the diabetic state, (2) the degree of control, (3) the severity of the disease, (4) the analytic serum cholesterol levels, or (5) the dietary intake of fat per unit of body weight.

CARROLL, FRANK D. *(Dept. of Ophth., Coll. of Physicians and Surgeons, Columbia Univ., and Inst. of Ophth., Presbyterian Hosp.)*: Optic neuritis. Am. J. Ophth. 35:75-82, January 1952.

An analysis of 240 cases of optic neuritis showed that they could be divided into three groups. In the first group (one-third) the condition was associated with diseases of adjacent structures, toxic agents, generalized infections or noninfectious conditions, Leber's disease, and vascular disease. In the second group (one-third) optic neuritis was due to multiple sclerosis or allied neurologic disorders. The causes in the last group were

Vascular disease is becoming a more common cause of optic-nerve involvement because more people now live to an older age. Vascular spasm as well as organic changes may be present. Diabetics seem to develop similar vascular changes at an earlier age. Patients with hypertensive vascular diseases also develop vascular diseases of the optic nerve at an earlier age; the average age was 54 years in this series.

CEDERQUIST, D. C.; BREWER, W. D.; BEEGLE, R. M.; WAGONER, A. N.; DUNSING, D.; AND OHLSON, M. A. *(Michigan State Coll., East Lansing)*: Weight reduction on low-fat and low-carbohydrate diets: I. Clinical results and energy metabolism. J. Am. Dietet. A. 28:113-16, February 1952.

On a low-fat diet, the subjects reported lack of "pep" throughout most of the study. They were discouraged because they were always conscious of being hungry. Without exception, the low-carbohydrate reducing diet resulted in satisfactory weight losses when the subjects adhered to it. The subjects reported a feeling of well-being and satisfaction. Hunger between meals was not a problem. Weight losses up to 33 kg. (unpublished data) did not result in flabbiness of tissues or looseness of skin.

CHANIS, ROLANDO *(Panama)*: Experience with a new insulin preparation, NPH 50. Presented at the Pan-

American Academy of Medicine, August 16, 1951. Pamphlet published by the author.

Results obtained in 7 cases are presented.

CLARKE, W. T. W. *(Univ. of Toronto and Toronto Gen. Hosp.)*: Diabetes surveys. Ontario M. Rev. *19*:99-101, February 1952.

In a review of 118 patients treated for diabetic acidosis at the Toronto General Hospital from 1943 to 1950, 12 were previously undiagnosed diabetics. Five of these died. Here is the extreme of delayed diagnosis and its results. Statistically valid evidence for the value of control in preventing the late complications of retinal lesions (which may produce blindness) and of nephropathy (which may lead to uremia) is now appearing from different groups of investigators. This applies particularly to patients whose diabetes began at an early age and who often have young families. Their illness or death is a great family and community tragedy.

COLLENS, WILLIAM S.; ZILINSKY, JAMES D.; GREENWALD, JEROME J.; AND STERN, ARTHUR B. *(Diabetic Res. Lab. and Med. Serv. of the Maimonides Hosp., Brooklyn, N. Y.)*: A new liver extract derived from pregnant mammalian liver. I. Its effect on peripheral neuropathy. Am. J. Med. *12*:53-58, January 1952.

The authors used a new extract derived from pregnant mammalian liver which they believe has the property of reversing the symptom complex of diabetic neuropathy. A series of 127 diabetics with manifestations of neuropathy were treated by daily intramuscular injection of 5 cc. of pregnant mammalian liver extract. In most cases the injections were continued for two weeks. Ninety-four per cent experienced reversibility of symptoms. Of these, 84 per cent showed good to excellent results, and 10 per cent had a fair result. Six per cent of the series failed to show any response to this therapy. A two-week course of therapy usually sufficed to produce a remission lasting between 2 and 6 months. Resumption of therapy during the relapse generally effected a prompt remission. Several illustrative cases are cited.

COPENHAVER, J. H.; SHIPLEY, ELVA G.; AND MEYER, ROLAND K. *(Univ. of Wisconsin, Madison)*: Enzymes in the tissues of alloxan-diabetic rats. Arch. Biochem. *34*:360-71, December 1951.

Data have been presented comparing the activities of anaerobic glycolysis, the tricarboxylic acid cycle, pyruvate oxidation, succinic dehydrogenase, glutamic dehydrogenase, and aspartic-glutamic transaminase in tissues of normal and alloxan-diabetic rats. Of these enzyme systems, all except glutamic dehydrogenase were found to be increased significantly in the livers of alloxan-diabetic rats. The increases in activity of the various enzymes in the liver of the diabetic rat are discussed with regard to changes in metabolism occurring in diabetes.

DAILEY, MORRIS E.; AND BENSON, RALPH C. *(Univ. of California Sch. of Med., San Francisco)*: Hyperthyroidism in pregnancy. Surg., Gynec. & Obst. *94*:103-09, January 1952.

Hyperthyroidism causes a rapid diminution in the glycogen stores in the liver and increases the ketone bodies in the urine. Hyperadrenalism, with a decreased insulin effect, is also noted. Theoretically these factors might encourage the development of a toxemia of pregnancy or might exaggerate a mild pre-eclampsia which under ordinary circumstances would not reach serious proportions.

DANA, GEORGE W.; EVERSOLE, STANTON L.; AND ZUBROD, CHARLES G. *(Johns Hopkins Univ. Sch. of Med. and Johns Hopkins Hosp. Baltimore)*: Hyperglycemia and its relationship to diabetic retinitis and glomerular nodules: A preliminary report. Bull. Johns Hopkins Hosp. *90*:98-99, January 1952.

The authors have concluded that patients with capillary aneurysms of the retina have hyperglycemia but do not require exogenous insulin to prevent the accumulation of ketone bodies. They postulate that the hyperglycemia without acidosis in this group of patients has a different mechanism than simple insulin deficiency. Relative excess of hyperglycemic-glycogenolytic hormone from the islets of the pancreas could explain the presence of hyperglycemia without acidosis in this group of patients.

DUNCAN, GARFIELD G. *(Jefferson Med. Col., Med. Div. of the Pennsylvania Hosp., and Benjamin Franklin Clin., Philadelphia)*: Practical use of the various insulins in the management of diabetes mellitus. Metabolism—Clinical and Experimental *1*:101-10, March 1952.

The author considers it inadvisable to treat obese diabetic patients with insulin except during acute complications. Simplification of insulin therapy without sacrifice of efficiency is urged in the treatment of patients with severe diabetes. On the basis of the demonstrated relative effects of the various insulins and the relative severity of the diabetes, 3 plans of insulin therapy are presented: (1) a single daily dose of globin insulin or of NPH insulin, (2) a single daily injection of a mixture of NPH and regular insulins, and (3) a mixture of NPH and regular insulins before breakfast and a small dose of NPH insulin before or after supper.

EDITORIAL: Campaign against diabetes. Bol. Asoc. méd. Puerto Rico *43*:561, October 1951.

This year, a group of Puerto Rican medical men organized a diabetes committee as part of the Puerto Rican Medical Association, with the purpose of initiating a campaign against diabetes similar to that being conducted in the United States. This activity has the backing of the directors and delegates of the Puerto Rican Medical Association, and support has been offered by the health commissioner (a member of the A.D.A. as well as of the newly formed diabetes committee), the governor of Puerto Rico, the local press and radio for publicity purposes, and various private groups and interested individuals. The members of the Association are responding enthusiastically to the call of their president, and local chapters of the committee have already been organized in Arecibo, Aguadilla, Arroyo, Bayamon, Cabo Rojo, Humacao, Lajas, Mayagüez, San German, and San Juan.

EDITORIAL *(Committee on Emergency Medical Care of the American Diabetes Association, Inc.):* Emergency medical care of diabetics in civilian defense. J.A.M.A. *147*:1350-54, December 1, 1951.

With the co-operation of the insulin manufacturers of the United States and Canada, data have been assembled concerning the present inventories of insulin, their distribution and storage, and the prospects for maintaining supplies in the event of wartime disaster. Owing to the nature of insulin preparations and the legal standards which have been set up for their storage, stock-piling of insulin in the usual sense does not appear practical at the present time. The urgency for the immediate education and training of civilians in preparation for a possible attack is admitted by all familiar with the problem. The American Diabetes Association, its affiliate associations, and state and county medical societies all should be deeply concerned with an educational program for diabetics. The information should be in simple form which could be printed as a handbill. An example is suggested.

EDITORIAL *(England):* Blood insulin. Brit. M. J. 2:1572, December 29, 1951.

It is now generally recognized that diabetes mellitus is by no means uniform in its characteristics and, presumably, in its causation. Considerable interest has been aroused by the results recently obtained in studying the plasma insulin level in diabetic patients. The key to this investigation of blood insulin was the development of a highly sensitive test animal—the rat made diabetic by alloxan and deprived of the pituitary and adrenals so that endogenous hormonal influences on the blood sugar level are minimized (A.D.H.A. rat). It has been found that as little as 0.05 milliunits of insulin depressed the blood sugar of such animals. Plasma from some untreated diabetic patients who had previously ingested glucose had a hypoglycemic activity, presumably due to the presence of insulin, which was not grossly subnormal in amount; but plasma from certain others had no detectable hypoglycemic activity. The striking observation has now been made that when diabetic patients are classified on clinical grounds into two main types, plasma insulin can be demonstrated in one type but not in the other. A further interesting and at present inexplicable observation is that some plasma samples which lack hypoglycemic activity in A.D.H.A. rats render the animals insensitive to insulin in a subsequent control test. It had been previously reported that plasma which lacked hypoglycemic activity did not mask the action of insulin added to the plasma sample. A marked hyperglycemic activity of the plasma has recently been noted in two acromegalic diabetics and might be attributable to the "hyperglycemic factor" which occurs in the pancreas. It would also be of interest to know whether the absence of hypoglycemic activity in plasma from insulin-resistant diabetics given a massive dose of insulin is due to the presence of an inhibitor in the plasma samples or to rapid removal of insulin from the patient's circulation. The quantitative validity of the results of the assay method under discussion appears to rest on the assumption that the slope of the response-log dose line and the sensitivity of the animals does not vary. This

aspect warrants careful investigation, particularly since a full statistical appraisal of the assay technic has not so far been published and since the amount of insulin present in the plasma of some of the diabetic patients was not greatly in excess of the minimum amount detectable by the technic. A useful adjunct to the A.D.H.A. rat technic would be the development of an in-vitro assay method which, although still impracticable for clinical use, would be more convenient and even more sensitive. The method based on phosphocreatine turnover appears to be rather insensitive, but promising results have already been obtained with a method based on the well-established effect of insulin on the uptake of glucose or of potassium by the isolated rat diaphragm.

EDITORIAL *(England):* Types of diabetes mellitus. Lancet *1*:653-54, March 29, 1952.

Young diabetics usually depend on administered insulin to prevent ketosis and are therefore thought to have a primary insulin deficiency, although the fact that they commonly require more insulin than pancreatectomized patients suggests that insulin lack may not be the only factor disturbing their carbohydrate metabolism. In contrast, diabetes coming on in later life, particularly in the obese, seldom calls for injections of insulin. In this instance, the mechanism is presumably either an excessive demand outstripping the intrinsic insulin supply or perhaps some factor opposing the action of insulin. The work of Bornstein and Lawrence on plasma insulin supports these familiar hypotheses and suggests that it may be possible sharply to divide diabetics into two categories —those with and those without an intrinsic supply of insulin. The fact that those with insulin are of the older age group would seem to preclude transition from the group with to the group without insulin, yet recent reports tend to undermine this superficially secure reasoning. Zubrod and colleagues have made a detailed study of the type of diabetes associated with the nodular intercapillary glomerulosclerosis of Kimmelstiel and Wilson. At necropsy on 190 diabetics, Zubrod and his associates distinguished three groups on the basis of the renal lesions: (1) those with Kimmelstiel-Wilson lesions, (2) those with other types of renal lesion, and (3) those with no renal disease. Clinically, the Kimmelstiel-Wilson group had differed from the other two in requiring progressively less insulin, although initially needing fully as much, and also in displaying virtually no tendency toward ketosis. On the basis of these findings, insulin was withdrawn from six patients who were thought to have Kimmelstiel-Wilson lesions. One of these was previously inadequately controlled on 50-130 units a day, yet he showed no ketonuria during 30 days without insulin despite the presence of an abscess and fever. Even though the patient was on a high-fat diet for four days, there was still no ketonuria or change in the CO_2 combining power of the blood. Again, in the other five cases, which were milder, ketonuria did not develop when insulin was withheld. The diabetes associated with Kimmelstiel-Wilson lesions seems to behave, therefore, as if there is not a complete lack of intrinsic insulin, although at the start it may be of the insulin-deficient type. Until we have reports of plasma insulin assays in such patients, we are left to wonder whether perhaps they are producing excessive quantities of glycogenolytic factor from the pancreatic alpha cells, which have also been credited with ketosis-preventing properties, or whether by an increased turnover rate of the Krebs tricarboxylic-acid cycle they dispose of the intermediates of fat metabolism with unusual efficiency.

EDITORIAL (EDITOR—W. R. FEASBY) *(Toronto):* Ontario M. Rev. *19*:36, February 1952.

Diabetes mellitus affects perhaps 150,000 Canadians, but only a small percentage of these have been recognized and placed under medical care. The activity by the Ontario Diabetic Association in co-operation with the National Sanitarium Association, both of which have mobile facilities to make case surveys, is most commendable.

EDWARDS, E. A. AND CRANE, C. *(Boston):* Lumbar sympathectomy for arteriosclerosis of the lower extremities. New England J. Med. *244*:199-204, February 8, 1951.

An analysis is presented of 100 cases of symptomatic arteriosclerosis of the lower extremities treated by lumbar sympathectomy. Twenty-seven were diabetics. Patients with necrosis down to bone proximal to the toes did so badly as to suggest that this finding constitutes the only definite contraindication to the operation. A moderately unfavorable influence was exerted by the presence of diabetes and a lesser influence by other visceral disease and perhaps also by extreme hypertension. The previous loss of the contralateral limb was an unfavorable factor.

ELMAN, R.; AND WEICHSELBAUM, T. E. *(St .Louis):* Significance of postoperative glycosuria and ketonuria in nondiabetic adults. Arch. Surg. *62*:683-97, May 1951.

It is inferred from the present study that there is little evidence of a serious disturbance in the carbohydrate metabolism in nondiabetic adults subjected to major surgical procedures and receiving feedings intravenously. However, the degree of glucose loss may reach 25 to 50 per cent of that injected. Excessive glycosuria may be harmful by producing transient dehydration.

EPSTEIN, SAMUEL H.: Clinical aspects of diabetic neuropathy. Arch. Neurol. & Psychiat. *67*:118-19, January 1952.

A series of 50 cases of diabetic neuropathy was analyzed from the standpoint of the role of vascular disease. Diabetic neuropathy from the prognostic standpoint is best classified as two types: that associated with arteriosclerosis, and that without demonstrable evidence of vascular disease. The latter type bespeaks a good prognosis, whereas in the former the prognosis is distinctly poor. This applies to the mononeuritic cases as well as to those of generalized neuropathy. Prolonged poor regulation of the diabetes in either type plays a role in the precipitation or aggravation of the neuropathy.

EROZ, KAMURAN; OZER, FIKRI; AND WINTERSTEIN, HANS *(Univ. Istanbul):* Blood sugar and liver glycogen in mammals with artificially lowered body temperatures. Arch. internat. pharmacodyn. *88*:63-83, October 1951.

In experiments performed on guinea pigs, rabbits, and cats, an attempt has been made to eliminate the mechanism of temperature regulation and to investigate the direct influence of the lowering of body temperature on blood sugar and on liver glycogen. To lower the body temperature without evoking regulatory mechanisms the animals were artificially cooled while in deep narcosis, or spontaneous fall in body temperature was brought about by cutting the lower cervical spinal cord. Artificial cooling to room temperature in deep narcosis provokes a strong hyperglycemia. The liver glycogen stays unchanged or sometimes is even increased considerably. If muscle shivering was observed, the blood sugar level in guinea pigs was not changed; in cats it was again increased, being accompanied this time by a decrease in liver glycogen. Injections of insulin are also effective in cooled animals. The hyperglycemic effect of cold and the hypoglycemic effect of insulin are algebraically summated and may entirely compensate each other. Injections of adrenaline are apparently without effect; there is no distinct difference between animals cooled only and those which are simultaneously treated with adrenaline. The hyperglycemia in cooled animals is the effect of pouring forth of adrenaline by way of the nervous system. The increase of blood sugar does not occur after the extirpation of the adrenal glands or after the section of the splanchnic nerves.

FARR, C. F.: Experimental study of the insulin polyvinylpyrrolidone complex. Rev. quím. farm. *8*:4-8, 1950 [Abstr. from Chem. Abstr. *45*:2582-83, March 25, 1951].

The addition of 25 per cent polyvinylpyrrolidone to a solution of insulin regulated and prolonged the hypoglycemic action in normal rats and diabetic human subjects.

FERRARA, MICHAEL A. *(Uncas-on-Thames Tuberculosis Hosp., Norwich, Conn.):* The tuberculous diabetic patient. New England J. Med. *246*:55-56, January 10, 1952.

Of 3,178 patients admitted to the Uncas-on-Thames Tuberculosis Hospital with pulmonary tuberculosis from July 1, 1937, to July 1, 1950, 68 (2.1 per cent) had associated diabetes mellitus. The prognosis for the diabetic tuberculous patient is graver than that for the tuberculous patient who does not have diabetes. All diabetics should have a chest x-ray examination at least every six months—or more often, if signs or symptoms warrant it.

FOSTER, G. E.; MACDONALD, JEAN; AND SMART, J. V. *(Wellcome Chemical Works, Dartford):* The assay of insulin in vitro by fibril formation and precipitation. Pharm. J. *167*:307, October 27, 1951.

In the reported work, the method of Waugh *et al.* was closely followed, with minor amendments. Reliable results were obtained in assays on freshly prepared samples of insulin, protamine zinc insulin, and concentrates representing the last 3 stages in the manufacture of crystalline insulin. The fibril precipitation assays failed, however, with a solution prepared with low potency insulin (11 I.U./mg.) and also with samples of globin zinc insulin. A significant discrepancy was found between the biological and fibril assay results for a 5½-year-old sample of

insulin. It was concluded that the fibril assay was applicable only under controlled conditions with preparations of substantially pure insulin.

GADDY, CLIFFORD G.; PARSON, WILLIAM; AND MULHOLLAND, H. B. *(Univ. of Virginia Hosp. Charlottesville, Va.):* Recognition and management of hypoglycemic states, with particular reference to islet cell tumors of the pancreas. Virginia M. Month. 79:124-31, March 1952.

Hypoglycemia due to islet-cell adenoma is discussed. Five cases are presented which illustrate several unusual features of the disorder. Symptoms of hypoglycemia due to islet-cell adenoma are not always progressive. A case is reported in which a remission of four years' duration followed exploration of the pancreas but in which no portion of the gland was removed. Subsequently, symptoms returned and an adenoma was found in the pancreas. Improvement in symptoms in another case was seen during the course of pregnancy. Weight loss rather than weight gain is sometimes seen in islet-cell adenomas.

GERRITZEN, F. *(Dept. of Endocrinology and Metabolism, Med. Service, Univ. Hosp., Leiden, Holland):* The duration of the action of the various insulins. Brit. M. J. *1*:249-50, February 2, 1952.

In a study of the action of various insulins in normal, healthy students the author made the following observations: (1) Regular insulin (Organon). The blood sugar reaches its lowest point after 1 hour and returns to its starting point in 8 hours. (2) Protamine zinc insulin (Organon). A duration of action of 18 hours; no evidence of a duration of 48 hours or longer; the lowest point is reached in 5 to 8 hours. (3) Di-insulin (Novo)-Duration of action, 16 hours. The greatest increase in blood sugar is during the first 3 hours. (4) Iso-insulin (Novo). Duration of action, 17 hours. Rapid decrease of sugar in the first hour. The steep decrease within the first hour leads to the assumption that this preparation contains regular insulin; however according to Hallas Moller, this is not the case. (5) Globin insulin (Burroughs Wellcome). Action is identical with that of di-insulin. (6a) NPH 50 (Organon). Duration of action, 11 hours. Lowest point after 4 hours. (6b) NPH 50 (Lilly). Duration of action, 11 hours. Lowest point after 3 hours. (7) Insulin mixtures (Organon). The impression is gained that the duration of action of the mixture depends upon the regular insulin content only so far as the decrease during the first three hours is greatest with the mixture containing the most regular insulin (the 3:1 mixture) and that thereafter the blood sugar takes longer to come back to the starting point than with the 2:1 and 1:1 mixtures. This would explain the longer duration of the action with a higher regular insulin content.

GORNALL, R. GUEST *(Warrington, England):* Correspondence: Action of different insulins. Brit. M. J. *1*:440, February 23, 1952.

The author briefly discusses the various types of insulin and warns against the assumption that long-acting insulins, with relation to their time of action, affect every diabetic in the same manner. It is a known fact that many diabetics fear hypoglycemic reactions more than the disease itself.

GRAY, C. H.; AND ILLING, ELIZABETH K. B. *(King's Coll. Hosp., London):* Plasma and urinary amino-acids in diabetes. J. Endocrinol. *8*:44-49, January 1952.

The aminoaciduria present in some cases of diabetes appears to be unrelated to the type or stage of diabetes but seems to accompany ketosis. Low plasma concentrations of amino acids were not observed, so that these results cannot be explained on the basis of a lowered renal threshold. The increased excretion of amino acids must be due either to increased production or to decreased utilization. There is no evidence of this latter possibility, for the urea excretion was not low, nor was the high concentration of amino acids in the plasma related to renal insufficiency. Ketosis thus seems to be associated with the production of free amino acids in excess. These are usually excreted by the kidney; if the ketosis is so severe that the kidney is unable to excrete them rapidly enough, however, the concentration in the blood increases. In fasting diabetic patients, the increased concentration of amino acids in the body fluids could be due either to a diminished activity of growth hormone or to an overaction of the adrenocorticotrophic hormone. Since ketosis is accompanied by increased excretion of adrenocortical hormones, it is possible that the increased production of amino acids observed in patients with ketosis may be related to excess adrenocorticotrophic activity of the anterior pituitary.

GRIEVE, W. S. M.; DE ROSARIO, A.; AND PETROW, V. *(Res. Labs., British Drug Houses Ltd., London, N. 1):* Insulin and related topics: Part I. Some observations on the causation of dermal reactions by insulin. J. Pharm. & Pharmacol. 3:883-86, December 1951.

Examination by the liver-slice technic of 3 samples of insulin known to produce dermal irritability on injection has failed to reveal the presence in them of the hyperglycemic-glycogenolytic factor. It therefore appears that this factor is not implicated in the causation of dermal reactions to insulin.

GUTFREUND, H. *(Dept. of Colloid Science, Univ. of Cambridge, Cambridge, England):* The reversible dissociation of insulin and its minimum molecular weight. Biochem. J. 50:564-69, February 1952.

It has been shown that the degree of aggregation of insulin in solutions depends not only upon *p*H, temperature, and insulin concentration but also upon the electrolyte concentration and the type of electrolyte present in the solution. At the optimum *p*H for dissociation (*p*H 2.5-2.7) the molecular weight calculated from osmotic-pressure measurements extrapolated to zero protein concentration is about 12,000 irrespective of salt concentration. The molecular weight at finite protein concentration is, however, larger the greater the salt concentration. There is some indication that sodium chloride has a more marked effect on the aggregation than phosphates. The sedimentation constant of insulin under conditions of maximum dissociation was found to be 1.65×10^{-18}, which is likely to be the sedimentation constant for the homogenous unit of M=12,000. Some general features of reversible changes occurring in solutions of crystalline proteins are discussed together with structural information which can be adduced from them.

HEALD, P. J. *(Rowett Res. Inst., Bucksburn, Aberdeenshire, Scotland):* The fermentation of pentoses and uronic acids by bacteria from the rumen contents of sheep. Biochem. J. 50:503-08, February 1952.

A procedure is described for the preparation of solid and liquid media which closely reproduce conditions in liquid from the rumen of sheep. With these media, 17 strains of gram-negative coliform rods of an indeterminate type have been isolated in pure culture. The products of fermentation (formic acid, acetic acid, lactic acid, ethanol, butyleneglycol, and acetoin) formed by five of these strains from xylose, glucuronic acid, glucose, and celloboise show marked differences in regard to both the substrate and the strain of organism used. The fermentation of xylose and glucuronic acid appears to follow a pathway different from that followed in the fermentation of glucose.

HEROLD, ARTHUR A., SR. *(Shreveport, La.):* Observations on diabetic therapy with special reference to insulin allergy. South. M. J. 45:360-64, April 1952.

There are 2 kinds of allergic reactions possible with insulin therapy; namely, that due to the protein of the animal from which the substance is extracted and that due to sensitivity to the insulin protein molecule, the latter being more serious and more difficult to overcome. Patients sensitive to the insulin molecule are allergic, in varying degree, to all insulin preparations. With proper care and patience, it is possible satisfactorily to desensitize even the severe reactors. When an allergic individual is taking one kind of insulin satisfactorily, caution should be used in changing the type and the change should never be made unless the patient is first tested for sensitivity.

HINKLE, LAWRENCE E., JR.; AND WOLF, STEWART *(Dept. of Med., New York Hosp.-Cornell Med. Center, New York City):* Importance of life stress in course and management of diabetes mellitus. J.A.M.A. 148:513-20, February 16, 1952.

Experimental evidence indicates that stressful life situations may lead to important metabolic changes in persons with diabetes mellitus and that these may be accompanied by emotional changes and changes in behavior. Ketonemia and an increased excretion of water, glucose, and chlorides were observed, as well as alterations in fasting blood sugar, which might lead to either hyperglycemia or hypoglycemia. Study of the life histories and daily experiences of persons with diabetes indicates that many of the apparently spontaneous fluctuations in the syndrome are the results of life stress. The similarities in the life histories of these diabetic persons suggest that developmental, cultural, and psychological factors may have an important influence on the onset and course of the disease. Treatment directed at alteration of the behavior and attitudes of the patient and his relation to his environment is helpful in abolishing otherwise uncontrollable fluctuations in the course of

labile diabetes and in preventing recurrent episodes of ketosis requiring hospitalization. In all cases of diabetes, an understanding of the patient and his life situation is necessary in order to understand the course of the disease, the limitations of therapy, and the goal which may be attained.

ITURBE ZABALETA, I.; RODRIGUEZ ARGUELLES, J.; AND PALACIOS BERMUDEZ, R. *(Mexico City):* Comparative study between NPH Insulin and the 2:1 mixture. Rev. méd. hosp. espan. *1*:29-36, 1951.

Under hospital conditions, 10 patients, treated with 2:1 mixtures of regular and protamine zinc insulin, were transferred to NPH insulin. Glycemic levels (venous blood) were determined ½ hour before breakfast and 1½ hours following lunch and supper. With a diet distribution of either 1/5, 2/5, and 2/5 or ¼, ½ and ¼ ("Mexican diet"), there was no significant difference in the glycemic levels recorded before or after the change in insulin treatment. The authors consider NPH insulin greatly advantageous from the practical point of view, since it obviates the mixing of different insulins.

JAUREGUI, RAUL HERNANDEZ *(Puebla, Mexico):* Clinical experience with a new type of modified insulin, NPH-50. La revista de medicina y ciencias afines *10*:3-12, August 1951.

Twelve patients were treated for 60 to 90 days with NPH insulin. Seven had been taking PZI; 2 had been receiving PZI and unmodified insulin; and 3 were new diabetics. When compared under similar dietary regimen with the other insulins, NPH provided as good or better control.

KADOTA, ICHIRO; AND MIDORIKAWA, OSAMU *(Kyoto Univ. Sch. of Med., Kyoto, Japan):* Diabetogenic action of organic reagents: Destructive lesions of islets of Langerhans caused by sodium diethyldithiocarbamate and potassium ethylxanthate. J. Lab. & Clin. Med. *38*:671-88, November 1951.

Twenty-four organic reagents capable of reacting with metal ions were examined for diabetogenic action in rabbits. Following intravenous injection of 500 to 1,000 mg. of sodium diethyldithiocarbamate per kilogram, all rabbits showed hyperglycemia immediately. Subsequently, 4 of 15 rabbits showed severe hypoglycemia after 8 to 12 hours, and they failed to recover after administration of glucose. After injection of 200 to 300 mg. of potassium ethylxanthate per kilogram in 15 rabbits, all animals showed hyperglycemia. One showed permanent hyperglycemia lasting 2 months. Three showed hypoglycemia 12 to 24 hours after injection, unrelieved by glucose. Lesions in the alpha and beta cells were correlated by the authors with the occurrence of either hyperglycemia or hypoglycemia. After injection of 5 to 500 mg. of thiosemicarbazide per kilogram, animals showed sudden convulsions, with hyperglycemia after 2 hours to 20 minutes. Although these animals survived temporarily following administration of insulin, they always died later. Islets of these animals appeared almost normal. Data are also presented on the effects of the other 17 compounds on blood sugar.

KEMP, A.; AND ZUIDWEG, M. *(Pharmaco-Therapeutic Lab., Univ. of Amsterdam):* A simple colour scale for the blood sugar determination according to Mendel and Hoogland. Acto physiol. et pharmacol. neerl. *2*:280-85, 1951-1952.

To simplify the practical application of the blood sugar determination according to Mendel and Hoogland a color scale has been designed, by means of which the glucose content of the blood can be determined directly, without the aid of a photoelectric colorimeter.

KEPINOV, L. *(Physiology Lab., Inst. of Physico Chemical Biology, Paris):* The role of the liver in the production of alloxan hypoglycemia. J. physiol., Paris *43*:97-101, No. 1, 1951.

The authors studied the effect of alloxan on the spontaneous glycogenolysis in the perfused liver of the rat. Alloxan causes a transitory diminution in the intensity of glycogenolysis. It is concluded that alloxan is an inhibitor of spontaneous glycogenolysis.

KUNTZE, JOACHIM; AND OTTO, HELLMUT *(Med. Clin. of the Gen. Hosp., Hamburg-Langenhorn):* The treatment of diabetic pruritus. Deutsche med. Wchnschr. *76*:1340-41, October 26, 1951.

It is believed that the intertriginous eczema of diabetic women is due to a chronically decompensated metabolism and frequently also to hormonal changes following

accepted dermatological methods, is dependent upon optimal control of the diabetes.

LACHANCE, ROBERT *(Hôpital Général de Verdun, Montreal):* How to diagnose diabetes clinically. Union méd. Canada *81*:299-304, March 1952.

The author reviews the common diagnostic procedures, stressing laboratory tests.

LAZARUS, S. S.; VOLK, B. W.; JACOBI, M.; AND GILADY, M. *(Jewish Sanatarium and Hosp. for Chronic Diseases, Brooklyn, N. Y.):* Absolute lymphocyte count and serum inorganic phosphorus after glucose administration in diabetic patients. Am. J. Clin. Path. *22*:127-33 February 1952.

Of 17 diabetic patients studied, 9 showed a change of the absolute lymphocyte count following administration of glucose which differed from that observed in the normal controls and 8 had a decline of the absolute lymphocyte count similar to that in the controls. All 9 patients with an abnormal lymphocyte response also had an abnormal response of serum inorganic phosphorus after administration of glucose. It is suggested that these findings indicate pituitary-adrenal dysfunction as the pathogenic factor of the diabetic syndrome in these patients.

Six of the 8 patients with a normal change of the absolute lymphocyte count also had a normal decline of serum inorganic phosphorus after glucose administration, suggesting a nonendocrine diabetes which is presumed to be due to hepatic dysfunction. The other 2 patients with a normal absolute lymphocyte response associated with an abnormal serum inorganic phosphorus response after glucose administration are believed to have a primary insulin-deficiency diabetes.

These finding support the results of a previous study that the absolute lymphocyte response to administered glucose might be employed to distinguish diabetes associated with disturbance of the pituitary-adrenal axis from diabetes due to other factors.

LENCIONI, LEO JULIO *(Rosario, Argentina):* Juvenile diabetes. Revista del Círculo médico de Paraná, September 1951.

A review of the subject is given, including evidence in different age groups, peculiarities of juvenile diabetes, laboratory procedures of diagnostic value, objectives and technic of treatment, complications, insulin resistance, diet, exercise, and education of patient and immediate family. A compilation is also made of the incidence of different complications.

LENS, J.; AND EVERTZEN, A. *(Res. Labs., N. V. Organon, Oss, Netherlands):* The difference between insulin from cattle and from pigs. Biochimica et biophysica acta *8*:332-38, March 1952.

Insulin from pig pancreas has been obtained in the pure state according to the solubility criterion. Its over-all amino analysis gives a result which does not differ sufficiently from that of cattle insulin to warrant the conclusion that the two are different. Their biological activity is equal. The solubilities at *p*H 6.4 differ slightly. The solubility curve of a mixture of the 2 shows that they form a solid solution. The only conspicuous difference is found in the composition of the "A" fractions of Sanger.

LICHTENBELT, H. VAN MACKEN; AND FLORIJN, E. *(Dept. of Med. and Lab. of Physiological Chemistry, Univ. of Utrecht, Netherlands):* Pyruvate content of blood and phosphorylation of thiamine in diabetic coma. Biochimica et biophysica acta *8*:349-50 March 1952.

When thiamin was administered to a patient in diabetic coma by intravenous injection, the thiamine pyrophosphate content of the blood slowly increased, just as in normal subjects, attaining a maximum several hours after the injection. Injected thiamine pyrophosphate disappears from the blood of normal persons as well as from that of the patients in 30 to 60 minutes. In diabetes, neither the breakdown of pyruvate nor the phosphorylation of thiamin is affected.

LICHTENSTEIN, HENRIK; GUEST, GEORGE M.; AND WARKANY, JOSEF *(Children's Hosp. Res. Foundation, Univ. of Cincinnati Coll. of Med., Cincinnati):* Abnormalities in offspring of white rats given protamine zinc insulin during pregnancy. Proc. Soc. Exper. Biol. & Med. *78*:398-402, November 1951.

Protamine zinc insulin administered to 51 pregnant nondiabetic albino rats throughout pregnancy in doses of 7 and 8 units daily (nearly the maximum dose

tolerated) had significant effects on fetal development. Compared with fetuses of untreated normal control rats, the average weight of the fetuses of the insulin-treated rats was lower and the number in each litter was less owing to fetal deaths and resorption. Mild skeletal abnormalities were found; many of the fetuses showed a decreased number or complete absence of ossification centers in the sternum, and a few showed some irregularities in shape and staining of the ribs and long bones.

LIEBER, MARSHALL M. *(Pathological Lab., Jefferson Med. Coll. and Hosp., and Philadelphia Gen. Hosp., Philadelphia):* The incidence of gallstones and their correlation with other diseases. Ann. Surg. *135*:394-405, March 1952.

This report is based upon an analysis of 26,895 consecutive autopsies performed at the Philadelphia General Hospital during a period of 20 years and of 7,771 consecutive autopsies performed at the Jefferson Medical College Hospital. A total of 1,259 cases of diabetes were studied in this series, and gallstones were present in 381 of them (30.2 per cent). An appreciable increase in the incidence of gallstones in diabetics occurred in each age group beyond the third decade and in each color of both sexes. There was a total increase in the incidence of gallstones in this disease of 77.4 per cent in white females, 84.5 per cent in white males, 348 per cent in colored females, and 183.1 per cent in colored males. In diabetics beyond 50 years of age, gallstones were present in approximately 1 of every 2 white females, 1 of every 3 colored females, 1 of every 5 white males, and 1 of every 7 colored males. The author's data do not furnish any demonstrable clues as to why an increased number of stones are found in diabetics, nor can any explanation be offered for the considerably greater increase in the incidence of gallstones in colored than in white diabetics.

LUFT, ROLF; AND SJÖGREN, BJÖRN *(Div. of Endocrinology of the Dept. of Med., Serafimerlasarettet, Stockholm):* A comparative study of the metabolic effect of adrenocorticotrophic hormone (ACTH), cortisone, and desoxycorticosterone acetate (DCA). Stanford M. Bull. 9:218-30, November 1951.

Studies were made of rheumatoid arthritis patients on a constant diet of known composition and on a constant fluid intake in a metabolic ward. The preparations used were ACTH protein of C. H. Li, an ACTH peptide mixture, cortisone, and DCA. The substances were administered intramuscularly 6 times daily. When ACTH protein was administered in doses of 3 to 50 mg. per day, there was marked initial retention of fluid, sodium, and chloride which lasted 3 to 4 days. There was a significantly increased excretion during continued hormone administration. When the ACTH treatment was discontinued, there was further excretion of fluid, sodium, and chloride. ACTH during the first day caused potassium loss, which was of the same magnitude in all doses. Part of the potassium loss may be due to decrease in total body protoplasm during ACTH treatment.

Cortisone was given in a dose of 200 mg. per day. This preparation did not give rise to the large initial changes which were seen with ACTH.

DCA given in a dose of 30 mg. daily caused retention of sodium and chloride only during the first week of treatment, followed by an increased excretion of sodium and chloride during the continued hormone supply. With ACTH and cortisone, as well as with DCA, a hypokalemic alkalosis with hypernatremia was achieved. Increased urinary excretion of total nitrogen and phosphorus was demonstrated during ACTH treatment. There was no significant difference in the changes brought about by doses of 13, 25, and 50 mg. of ACTH protein daily. Smaller doses did not influence the urinary excretion of nitrogen, calcium, and phosphorus.

MAASSEN, A. P. *(Pharmacological Lab., Univ. of Leyden, Netherlands):* Growth and metabolism. Arch. internat. pharmacodyn. *88*:434-41, January 1952.

New evidence in favor of a pancreatropic effect of growth hormone has been given by a decreased rise of the blood sugar level in dextrose-loaded animals.

MACKLER, BRUCE; AMMENTORP, PETER; GRAUBARTH, HARRY; AND GUEST, GEORGE M. *(Children's Hosp. Res. Foundation, Univ. of Cincinnati, Cincinnati):* Glucose formation by kidneys in eviscerated dogs. Proc. Soc. Exper. Biol. & Med. 78:479-80, November 1951.

In 5 dogs subjected to evisceration and bilateral nephrectomy, the rate of disappearance of sugar from the blood immediately after operation was nearly double the rate observed in 5 dogs similarly eviscerated but not nephrectomized. This indicates that in hepatectomized dogs the kidneys may be an important source of sugar supplied to the blood stream.

NATH, MADHAB CHANDRA; AND CHAKRABARTI, CHITTA HARAN *(Univ. Dept. of Biochemistry, Nagpur, India):* Acetoacetate-induced changes in blood lactic and blood ascorbic acids; prevention by insulin and amellin. Proc. Soc. Exper. Biol. & Med. 78:369-71, November 1951.

Sodium acetoacetate was injected daily by the intraperitoneal route into normal rabbits in increasing doses from 25 to 175 mg./kg. The blood lactate level rose from an average of 7.9 mg./100 cc. to 36.7 mg./100 cc. after 90 days. Simultaneous injection of amellin prevented the accumulation of blood lactate. In animals which had received sodium acetoacetate for 90 days, amellin restored the blood lactate level to normal within 40 days, despite the continued injection of increasing amounts of the acetoacetate. In an experiment otherwise identical, insulin was not as effective as amellin, the blood lactate diminishing initially but later increasing. The insulin-treated animals were not as healthy as the amellin-treated ones. The injection of acetoacetate also reduced the plasma ascorbic acid from 2.5 to 0.83 mg./100 cc. after 60 days.

NOSSAL, P. M. *(Dept. of Biochemistry, Univ. of Sheffield, Sheffield, England):* The effects of glucose and potassium on the metabolism of pyruvate in *Lactobacillus arabinosus.* Biochem. J. 50:591-95, March 1952.

Anaerobically, washed suspensions of *L. arabinosus* require glucose, potassium chloride, and manganous chloride for maximum rates of pyruvate decomposition. The amount of pyruvate utilized is accounted for by the formation of carbon dioxide and acetoin. Aerobically, different batches of cell suspensions differ in their Q_{O_2} values with pyruvate as substrate, the Q_{O_2} varying from 10 to 50. Cells with high Q_{O_2} values require only the addition of manganous chloride for the maximum rates of pyruvate utilization; cells with low Q_{O_2} (oxygen quotient) values require glucose, potassium chloride, and manganous chloride for full activity. Glucose acts catalytically, depresses oxygen consumption, and increases acetoin formation. Potassium chloride is effective only in cells which also require glucose for maximum activity. Fructose and galactose accelerate pyruvate utilization and increase acetoin formation but less effectively than glucose. No acetoin is formed from sugars, glyceraldehyde, lactate, of acetaldehyde; lactate and acetaldehyde do not increase acetoin formation from pyruvate. Pyruvate utilization is more rapid in citrate-phosphate buffers than in acetate buffers of the same *p*H; phthalate inhibits strongly. Aerobically, the *p*H optimum of the reaction is about 4.6; anaerobically, about 3.7. Cell suspensions rapidly lose their ability to decompose pyruvate anaerobically without added glucose; the ability to decompose pyruvate aerobically, or anaerobically in the presence of glucose, is retained for several days at 2°, especially when the cells are suspended in 0.1M potassium chloride.

OSIO DAVID *(Asunción, Paraguay):* NPH insulin—its therapeutic action in diabetes mellitus. Bol. agrup. med. est. *4*:3, January 1952.

NPH insulin was used in 34 cases (4 severe, 14 moderate, and 16 mild). In the moderate and mild cases, satisfactory control was obtained with one single daily dose. Three of the severe cases could also be controlled with one daily injection, whereas the fourth needed additional regular insulin.

OTTO, HELLMUT *(Med. Clin. of the Gen. Hosp. Hamburg-Langenhorn):* The importance of fasting blood sugar in evaluating the status of metabolism in diabetics. Deutsche med. Wchnschr. 76:1297-99, October 19, 1951.

In mild and moderate diabetics with optimal fasting blood and urine sugar levels, the peak values of the daily blood sugar profile usually lie below 250 mg. per cent and rarely exceed 275 mg. per cent. It is the author's opinion that this margin of fluctuation is permissible. For the control of mild and moderate cases, daily blood sugar profiles are not considered necessary. In severe, labile cases of diabetes mellitus, such a close relationship between fasting blood sugar, urine sugar, and the daily blood sugar profile usually does not exist. Such patients require repeated determinations of the daily blood sugar profile. In the interval between their performance, determinations of fasting blood sugar levels are of value. The physician who is taking charge of the case after the patient's discharge from the hospital must have full information on any peculiarities in his metabolism. Frequently, repeated fasting blood sugar, urine sugar, and urine acetone determinations will suffice for the early detection of any metabolic variations. The same applies to diabetics with kidney damage. Because of the availability of better chemodiagnostic methods, treatment of deranged metabolism, as well as any changes in insulin dosage in labile diabetics and those with kidney damage, should be undertaken in the hospital.

PALEY, RONALD G. *(Univ. of Pennslyvania, Philadelphia):* Dermal reactions to insulin. The Pharmaceutical Journal of the Pharmaceutical Society of Great Britain, *168*:80, February 2, 1952.

The residue obtained from the mother liquors after repeated recrystallizations of an insulin known to cause dermal reactions was concentrated and a solution prepared. Intravenous injection of this impure fraction and of various insulins shown to produce skin reactions into fasted and trained rabbits did not show a hyperglycemic factor. A cross-over test also gave a negative result. From the work quoted in this paper it is obvious that the hyperglycemic-glycogenolytic factor is not responsible.

PFEIFFER, E. F.; SCHÖFFLING, K.; AND WEICHENHAIN, H. *(1st Med. Clin., Univ. of Frankfurt a.M., Germany):* The effect of insulin administration on circulating eosinophils in normal and diabetic individuals. Klin. Wchnschr. 30:56-59, January 15, 1952.

The eosinopenia which occurs in normal individuals as a result of the "stress" hypoglycemia (Selye's adaptation syndrome) following administration of insulin is seen only in those diabetics who are sensitive to insulin. In the so-called "regulatory" diabetes, as well as in "primary hyperglycemia," the decrease in circulating eosinophils corresponds to the rise in blood sugar, and a blood sugar curve results which is inversely proportional to the eosinophil response. The mechanism of this reaction and the release of anti-insulin hormones from the adrenal glands are discussed.

PINCUS, JOSEPH B.; NATELSON, SAMUEL; AND LOGOVOY, JULIUS K. *(Jewish Hosp. of Brooklyn, Brooklyn, N.Y., and the Rockford Mem. Hosp., Rockford, Ill.):* Effect of epinephrine, ACTH and cortisone on citrate, calcium, glucose and phosphate levels in rabbits. Proc. Soc. Exper. Biol. & Med. *78*:24-27, October 1951.

Epinephrine (0.25 mg.) subcutaneously caused a rise in calcium, citrate, and glucose levels and a fall in phosphate and potassium levels. Cortisone (25 mg./Kg.) intramuscularly caused a rise in glucose and phosphate levels and a fall in calcium and citrate levels. ACTH (0.3 to 0.6 mg./Kg.) intramuscularly caused a rise in citrate and a fall in calcium levels. The authors suggest that the balance between ACTH, epinephrine, insulin, and cortisone secretion, because of their effect on citrate, calcium, and phosphate levels, plays a significant role in the maintenance of the calcium ion concentration of the plasma.

POLLACK, HERBERT; AND BOOKMAN, JOHN J. *(Mt. Sinai Hosp., New York City):* Riboflavin excretion as a function of protein metabolism in the normal, catabolic and diabetic human being. J. Lab. & Clin. Med. 38:561-73, October 1951.

Riboflavin and nitrogen balances were correlated by the authors in nutritionally normal individuals, in patients in the postoperative convalescent period, and in diabetics maintained on insufficient amounts of insulin. The nutritionally normal individuals usually retained more than 50 per cent of the ingested riboflavin when in nitrogen balance and less than 50 per cent when in negative balance. Intense negativity of nitrogen balance precipitated by surgical procedures in the nondiabetic subject or by insulin withdrawal in the diabetic patient was associated with an excretion of riboflavin many times greater than the ingested amounts. Nitrogen equilibrium and positive nitrogen balances were associated with normal riboflavin excretions even in the presence of marked glycosuria.

PORTUONDO Y DE CASTRO, JUAN M.; AND CANO, R. MUNIZ *(Havana):* ACTH therapy in 2 cases of rheumatoid arthritis and psoriasis coexisting with diabetes mellitus. J. Clin. Endocrinol. & Metabolism *12*:361-64, March 1952.

ACTH proved strikingly effective in inducing a complete clinical and biological remission of rheumatic symptoms and some improvement of the cutaneous lesions in 2 cases of psoriatic arthritis complicated by diabetes mellitus. Carbohydrate tolerance was impaired, as expected. The fasting blood sugar rose to 181 mg. per 100 cc. in the first case, in which there was no change in the PZI dosage, and to 194 mg. in the second case, in which the I-PZI dosage had to be doubled in order to keep the patient symptom-free. The associated diabetes mellitus did not prove to be an insurmountable contraindication to ACTH therapy for the arthritis.

POTH, EDGAR J.; AND FROMM, STANLEY M. *(Surgical Res. Lab., Dept. of Surg., Univ. of Texas Med Branch, Galveston):* The relation of pancreatic secretion to peptic ulcer formation. Southwestern Med. 16-18, January 1952.

The external secretion of the pancreas is important locally to neutralize hydrochloric acid for direct protection of the mucous membrane of the duodenum and to block the secondary release of hormones which lower blood sugar and thus stimulate the vagus via the nucleus dorsalis. There seems to be abnormal carbohydrate metabolism in a certain proportion of individuals suffering from peptic ulcer. Thus, the internal secretion of the pancreas might well be important in the development and maintenance of peptic ulceration. Our information is still fragmentary, and further studies are necessary before reasonably accurate answers will be available as to the importance of carbohydrate metabolism in peptic ulcer formation.

PROCOPIO, J. (*Rio de Janeiro*): Modern trends in the treatment of diabetes mellitus. Bol. Cent. est. Hosp. serv. est. pp. 1-14 (rep.), November 1951.

This review includes present trends in diet, the different insulins, and complications.

PRUNER, G.:Rapid estimation of biological activity of insulin (preparations) by ability to reduce potassium ferricyanide. R. C. 1st. super. sanit. *13*:127-41, 1950, [Abstr. from Brit. Abstr., C:223-24, June 1951].

The insulin is oxidized in alkaline buffer and the remaining ferricyanide estimated spectrophotometrically by absorption at 420 *mμ*. An empirical relationship is established between biological activity of several commercial insulin preparations and the amount of potassium ferricyanide reduced.

RABINOWITCH, I. M. *(Montreal):* Experiences with a new liver extract for the treatment of diabetic neuropathies. Am. J. Med. *12*:59-65, January 1952.

In treating the symptoms of diabetic neuropathy with pregnant mammalian liver extract, the author reports favorable results similar to those obtained by W. S. Collens and his associates. In 36 cases so treated, only 3 failed to respond. Illustrative cases are described.

RAMIREZ PANE, R. *(Hosp. de Clinicas da Faculdade de Medicina de Assunção, Paraguay):* Vascular complications in diabetics encountered in the medical clinic. Brasil-med. *65*:525-46, December 1-15, 1951.

The author reviews a group of 119 diabetics, 35 of whom presented vascular complications.

RAMIREZ PANE, RUBEN *(Asunción, Paraguay):* Complications of diabetes in clinical medicine. Brasil-med. *65*:567, 1951.

The author presents 14 case histories of diabetes complicated by nephritis, cystitis, retinopathy, and heart disease.

RECHT, LEOPOLD *(Aalborg, Denmark):* Kimmelstiel-Wilson's syndrome in juvenile diabetics. Nord. med. *50*:1855-58, December 12, 1951.

The purpose of the investigation was to determine the incidence of Kimmelstiel-Wilson's syndrome in a Danish series of juvenile diabetics. The series comprised 31 cases which were under observation for at least ten years. At the follow-up, 6 of the patients had died. Their average age at the onset of diabetes was 12.7 years, and the average age at death was 27.3 years. Two died of uremic coma (1 of these showed Kimmelstiel-Wilson's syndrome, and intercapillary glomerulosclerosis was verified at autopsy); 3 died of pulmonary tuberculosis; and 1 of diabetic coma. Of the 25 survivors, 24 were objectively examined. These 24 reached an average age of 27.4 years, and the average duration of diabetes was 15.6 years. The following data were found on examination: 12 had albuminuria; 8, edema; 8, urea clearance less than 45; 6, hypertension (blood pressure greater than 150/100); 16, retinal hemorrhages; 4, serum cholesterol levels greater than 300 mg. per cent; 6, hemoglobin per cent less than 75. Four patients, or one-sixth, had no symptoms. A correlation was demonstrated between kidney and eye symptoms. It was not possible to prove any relation between the incidence of complications and diabetes control, or between the former and the type of diet. The investigation confirms the frequent existence of late vascular complications in juvenile diabetes of long duration.

REID, E. *(Sch. of Biochemistry, Univ. of Cambridge, England):* Diabetogenic activity as an inherent property of growth hormone. J. Endocrinol. 8SEJ-EE, January 1952.

The reported experiments suggest that the diabetogenic and growth-promoting activities of growth hormone are to be attributed to the same structures in the same protein molecule.

ROBERTSON, J. DOUGLAS; AND KIRKPATRICK, H. F. W. *(Dept. Clin. Invest. The London Clinic, London):* Simmond's disease (hypopituitarism) in a man, due to traumatic hemorrhage into the pituitary gland. Lancet *1*:1048-51, May 12, 1951.

A case of Simmond's disease in a man was caused by an acute lesion, probably due to hemorrhage, in the pituitary gland. No similar case has been traced. The differential diagnosis seemed to be between anorexia nervosa, Addison's disease, myxedema, and Simmond's disease. In favor of the latter were the sudden onset following an accident, the typical signs and symptoms, the failure of function of the thyroid, adrenals, and gonads, and the degenerative changes in hair, skin, and teeth. The insulin tolerance test, even when done with so small an intravenous injection of insulin as 0.03 unit per kg. of body-weight, is not without risk. A dangerous hypoglycemia can develop, the blood sugar level falling from 75 to 15 in 25 minutes.

ROBINSON, JAMES W. *(Pennsylvania Hosp., Philadelphia):* Coronary thrombosis in diabetes mellitus. New England J. Med. *246*:332-35, February 28, 1952.

Data are presented in an analysis of 54 cases of coronary thrombosis occurring in diabetics. The frequently demonstrated predilection of diabetic women to coronary atherosclerosis is re-emphasized. If the admissions to the Pennslyvania Hospital are a sample of the general population, the data suggest that approximately 1 of 5 women with coronary thrombosis is a diabetic and that a diabetic woman is 14 times as likely as a nondiabetic woman to suffer from coronary thrombosis. In general, the women seemed to have less recuperative power. It also appeared that obesity and diabetes of long duration were slightly unfavorable factors.

RODRIGUEZ-CANDELA, J. L. *(Inst. de Med. Exper., Madrid):* The hyperglycemic-glycogenolytic factor produced by the pancreas. J. Clin. Endocrinol. & Metabolism *12*:245-46, February 1952.

The author's experience indicates that the pancreatic enzymes do not play a role in the reduced insulin requirement of the alloxan-diabetic dog after pancreatectomy, and he feels that the pancreas probably produces some factor which is responsible for the difference in the insulin requirement.

ROOT, HOWARD F. *(Joslin Clin., New England Deaconess Hosp., and Dept. of Med., Harvard Med. Sch., Boston):* Degenerative complications of diabetes: A review. J. Clin. Endocrinol. & Metabolism *12*:458-79, April 1952.

A review is given of present concepts regarding the nature, treatment, and prevention of certain major degenerative complications of diabetes mellitus. Although, among vascular lesions, atherosclerosis remains the predominant cause of death, the lesions in the arterioles, in the venules of the retina, and in the capillaries seem equally specific for diabetes. The neuropathies of diabetes involve the autonomic and central nervous systems rather than peripheral nerves alone. Diabetic nephropathy, including the Kimmelstiel-Wilson syndrome, and diabetic retinopathy are directly related to the severity, duration, and control of diabetes. A new pathologic concept would relate the hyaline changes in the walls of capillaries and arterioles, in the renal glomeruli, and in the islands of Langerhans to disturbances in metabolism of polysaccharides or polysaccharide complexes.

ROSE, THOMAS F. *(Royal North Shore Hosp., Sydney):* Pancreatitis complicated by pseudocyst: Report of a case of a patient dying in diabetic coma. M. J. Australia *2*:854-56, December 22, 1951.

A case of chronic pancreatitis which was complicated by a pseudocyst is described. The disease was progressive, and the patient died in diabetic coma 4 months after the pseudocyst was drained. Four other cases of pseudocyst are also briefly described.

ROSS, E. J. *(Inst. of Ophthalmology, London):* The influence of insulin on the permeability of the blood-aqueous barrier to glucose. J. Physiol. *116*:414-23, April 28, 1952.

nonelectrolytes of equivalent ether/water partition coefficient. A possible mechanism for this preferential rate of entry has been investigated in the rabbit by a comparison of the rate of penetration of glucose in normal rabbits, in alloxan-diabetic animals, and in animals receiving exogenous insulin. The existence of a special mechanism, enzymic in nature, for the activated diffusion of glucose across the blood-aqueous barrier is suggested, and the possibility that it is a phosphorylation-dephosphorylation system is discussed. It is emphasized that such an enzymic system is not intracellular but must be situated on the membranes of the cells constituting the blood-aqueous barrier.

ROWLINSON, H. R.; AND LESFORD, JOAN M. *(The AB. Insulin Assay Labs.):* An *in vivo* test for the hyperglycemic glycogenolytic factor in insulin. J. Pharm. & Pharmacol. 3:887-96, December 1951.

An in-vivo method has been described for demonstrating the presence of the hyperglycemic-glycogenolytic factor in insulin; by this method, the insulin can be administered in an unmodified form and significant responses may be obtained with a moderate dose. The results so far obtained with the technic described show that British and Danish insulin do not exhibit activity due to this factor. A linear relationship between the area under the blood sugar curve and the logarithm of the dose of the factor has been established.

SALDUN DE RODRIGUEZ, MARIA LUISA *(Montevideo):* NPH in infantile diabetes. El dia médico uruguayo 29:651-54, August 1951.

Fifteen patients being treated with 1:1 or 2:1 mixtures of unmodified and protamine zinc insulin were transferred to NPH insulin. In general, the total dose required to obtain similar control was less with NPH than with the mixtures. In 14 cases the control afforded by the new insulin was satisfactory; only one extremely severe case (in which all mixtures had failed to produce reasonable control) was not controlled by NPH insulin.

SCHNEEBERG, NORMAN G.; AND FINESTONE, ISRAEL *(Philadelphia):* The effect of age on the intravenous glucose tolerance test. J. Gerontol. 7:54-60, January 1952.

Normal subjects over 40 years of age exhibited a significant depression of tolerance to intravenously administered glucose when compared with normal subjects 16 to 39 years of age. This depression of glucose tolerance of the older subjects could not be attributed to liver dysfunction, deficient stores of available liver glycogen, or a previous low-carbohydrate diet. Certain factors that could not be controlled in this study were discussed, such as race, family history of diabetes, and the degree of physical activity of the subjects. The conclusion is tentatively offered that advancing age is associated with a depression of tolerance to intravenously administered glucose.

SCOTT, ORLAND B.; AND HARKINS, HENRY M. *(Div. of Surgery, King County Hosp. and the Dept. of Surgery, Univ. of Washington Sch. of Med., Seattle):* Pancreatic enzyme activity of peritoneal exudate collected by sump drainage. West. Surg. J. 59:619-25, December 1951.

Patients subjected to upper abdominal surgery in which pancreatic trauma occurred either prior to or at the time of surgery were studied with reference to the amylase content of peritoneal fluid obtained by sump drainage by the technic of Chaffin. In 17, or 33 per cent, there was an elevation of amylase content. In 13 cases studied for elevation of serum amylase, there was 1 elevation.

SCOVILLE, ADDISON B., JR. *(Nashville, Tenn.):* Complications of insulin therapy: Preferred procedures. J. Tennessee M. A. 45:23-25, January 1952.

A number of complications of therapy which should be recognized by all physicians are described.

SHUTE, W. E.; AND SHUTE, E. V. *(London, Canada):* Correspondence: Diabetic gangrene. Brit. M. J. 1:276, February 2, 1952.

The authors comment on the use of alphatocopherol in diabetic gangrene. They are convinced that patients given this substance benefit greatly and as a result frequently do not even need conservative surgery.

SILIPRANDI, DAGMAR; AND SILIPRANDI, NORIS (*Inst. of Biological Chemistry, Univ. of Rome, Italy*): Action of insulin on thiamine phosphorylation. Nature, London *169*:329, February 23, 1952.

In order to investigate whether or not insulin acts on the formation of cocarboxylase from thiamin, a study was made of its action on those forms of alloxan diabetes in which the phosphorylation of thiamin is nearly completely inhibited. Used in the study were severely affected diabetic rats in which the respiratory quotient was not increased after 1 to 1½ hours from the time of glucose + thiamin administration. Liver cocarboxylase content is increased in diabetic animals treated with thiamin + insulin, in contrast to those treated with thiamin alone. On the other hand, administration of insulin (20 I. U./kg.) to diabetic rats not treated with thiamin does not give rise to a significant increase in the cocarboxylase content when compared with findings in the untreated rats. The negative results obtained with insulin alone may be attributed to a low content of the thiamin in diabetic animals. Insulin enhances the thiamin phosphorylation in the diabetic animal when the latter has a sufficient amount of thiamin.

SOMOGYI, MICHAEL (*Lab. of the Jewish Hosp. of St. Louis, Mo.*): Notes on sugar determination. J. Biol. Chem. *195*:19-23, March 1952.

Two improved copper reagents for the quantitative determination of sugars are described—one for use in the colorimetric, the other for the iodmetric technic.

STAFFIERI, JUAN J.; AND CARDONNET, LUIS J. (*Rosario, Argentina*): Variable insulin mixtures in juvenile diabetes. Medicina, Buenos Aires 11:41-49, February 1951.

A review is made of the subject. An excellent degree of control could be obtained in 6 juvenile cases of diabetes with the use of tailor-made mixtures.

STERLING, REX E.; AND DAY, PAUL L. (*Dept. of Biochemistry, Sch. of Med., Univ. of Arkansas, Little Rock*): Blood sugar levels in alloxan-treated, galactose-fed, xylose-fed weanling rats. Proc. Soc. Exper. Biol. & Med. 78:431-33, November 1951.

Cataract was produced experimentally in weanling littermate rats by (1) alloxan treatment, (2) galactose feeding, and (3) xylose feeding. All groups showed greatly elevated blood-sugar levels as compared with untreated controls receiving glucose. Cataract was exhibited by all of the xylose-fed and galactose-fed rats and by nearly all of the alloxan-treated animals. However, the development of cataract was much slower in the alloxan-treated than in the other groups. Galactose or xylose feeding proved to be injurious to the lens at a lower blood sugar level. The authors conclude that not only the level of blood sugar but also the specific configuration of the sugar concerned was a factor in its cataractogenic action.

STETSON, RICHARD P. (*Boston and West Roxbury, Mass.*): The management of uncomplicated diabetes mellitus. M. Clin. North America pp. 1523-31, September 1951.

In simplest terms, the aims of diabetic management are to maintain the patient in a state of optimal well-being by providing a regular diet adequate in carbohydrate, protein, fat, minerals, and vitamins and to maintain a blood sugar within normal limits. Under certain circumstances, compromise with the ideal will result in a healthier and happier patient than will insistence upon complete normoglycemia. The training of a diabetic patient or the responsibility of the diabetic's physician does not rest with instruction of the patient as to how to plan his diet, how to test his urine, and how to give himself insulin under sterile precautions.

Every diabetic patient should also learn the principles of hygiene of the feet, the danger of infections and their influence on his toleration for carbohydrate, the symptoms and treatment of hypoglycemia, and the danger signals of acidosis. The physician, on the other hand, should have a thorough knowledge of the methods of treating these complications, the development and treatment of diabetic neuropathy, and the recognition and care of the degenerative vascular changes seen in diabetics.

However, a thorough understanding of what constitutes good routine day-by-day care of uncomplicated diabetes, diagnosed in its early stages and treated enthusiastically, will go far to avoid the development of those complications which bring the grief and tragedy that has all too often marked the course of poorly managed diabetes.

STUHLFAUTH, K.; AND PROSIEGEL, R. *(Univ. Med. Policlin., Munich):* Intermediary processes in carbohydrate metabolism following intravenous levulose administration in normal individuals, diabetics, and obese persons. Klin. Wchnschr. 30:206-09, March 1952.

The disassimilatory processes in carbohydrate metabolism following intravenous administration of levulose were investigated by observation of the changes in blood levels of glucose, fructose, lactic acid, pyroracemic acid, oxybutyric acid, acetone, and inorganic phosphate. The considerable acceleration of fructolysis (as compared with glycolysis), which occurred independently of insulin, permitted conclusions on various intermediary disturbances in diabetes, obesity, and liver parenchyma damage.

SYSI, R.: Retinal micro-aneurysms in connection with generalized diseases causing retinopathy. Brit. J. Ophth. 35:560-67, September 1951 [*Abstr. from* Am. J. Ophth. 35:146, January 1952].

Retinal microaneurysms are frequently seen in diabetes, arteriosclerosis, nephritis, and nephrosclerosis and are at times so similar in form that the diseases are indistinguishable ophthalmoscopically. These aneurysms have been studied in great detail in diabetes but not in the other diseases.

It is suggested that the aneurysms are not a result of hypertension, arterial or renal disease, or hyperglycemia but of a disorder in the central regulation of circulation which is common to all these diseases. This does not infer that these conditions are manifestations of the same disease but rather that there is some central dysfunction common to all.

TAYLOR, J. D.; RICHARDS, R. K.; AND DAVIN, JEANNE C. *(Abbott Lab., North Chicago, Ill.):* Excretion and distribution of radioactive S^{35}-cyclamate sodium (sucaryl sodium) in animals. Proc. Soc. Exper. Biol. & Med. 78:530-33, November 1951.

A study was made of the excretion and distribution of S^{35}-sucaryl in the tissues of the rat, dog, and rabbit. Cold isotope dilution and paperchromatographic methods showed that in the rat, at least 95 per cent of the material was excreted unchanged. Single doses up to 3.2 gm./kg. intraperitoneally were rapidly excreted by the rat in 24 hours. A dose of 1.4 gm./kg. was excreted with equal rapidity by normal rats and a unilaterally nephrectomized rat. With repeated oral administration in rats, about two-thirds of the dose was excreted in the feces and one-third in the urine. No significant amounts of S^{35}-sucaryl were found to be stored in the body. In the dog, only 0.5 per cent of the injected S^{35}-sucaryl was found in the bile 5 hours after an intravenous injection of 0.7 mg./kg.

With the exception of the kidney and perhaps the liver, the various organs of the rat, rabbit, and dog showed no significant concentration of the drug. Sucaryl penetrated the brain with difficulty but was found in the fetus of the rat.

THOMPSON, R. H. S.; AND WATSON, D. *(Dept. of Chemical Pathology, Guy's Hosp. Med. Sch., London):* The nitroprusside method for the determination of blood glutathione. J. Clin. Path. 5:25-29, February 1952.

One of the chief disadvantages in the use of the nitroprusside reaction for the quantitative determination of thiols has been the instability of the color. The addition of cyanide decreases the rate of fading, and in view of the reactivity of thiols with traces of metals the authors investigated the effect of the addition of potassium cyanide and of various metal-binding agents before developing the color. No observed effect was produced by potassium cyanide, 8-hydroxyquinoline, sodium diethyldithiocarbamate, or *a*-benzoin oxime ("cuppron") in the concentrations studied. The trichloroacetic acid extracts can safely be left for at least one hour at room temperature, without subsequent loss of color intensity, before the nitroprusside reaction is carried out. If the ammonia is not added immediately after the addition of the nitroprusside reagent, the color intensity produced is low. Unless the reaction is carried out at a carefully controlled temperature, it is inadvisable to attempt to work from any precalibrated standard curve; a standard GSH solution should, instead, be included in each series of estimations.

Since some workers are now interested in blood glutathione levels in diabetes, it is desirable to know whether any interference is to be expected from the slowly developing nitroprusside reaction given by acetoacetic acid. Amounts of acetoacetic acid roughly equivalent to blood levels of 4 mg./100 ml. gave no measurable color at 30 seconds, although by 90 seconds a significant degree of color had already developed; amounts of acetoacetic acid much above this level would of course interfere even at 30 seconds.

UHRY, PIERRE *(Paris):* Treatment of diabetes (practical points). Edit. Masson & Cie, Paris, 1951 [Abstr. from La Diagnosi 8:154, March 1952].

A review of modern concepts in the diagnosis and treatment of diabetes mellitus. Great emphasis is placed on laboratory procedures.

VALLANCE-OWEN, J. *(London Hosp., London):* Liver glycogen in diabetes mellitus. J. Clin. Path. 5:42-48, February 1952.

The liver glycogen has been studied histologically in 31 patients with diabetes mellitus dying in coma and compared with controls. It has been shown that diabetic ketosis and coma can occur with normal or increased glycogen deposits in the liver. Such normal or increased glycogen deposits are frequently found in untreated human diabetes mellitus. Pure insulin causes an increase in glycogen deposition in the liver. The bearing of these findings upon present conceptions of diabetes mellitus is discussed.

VILLEE, CLAUDE A.; WHITE, VIVIEN K.; AND HASTINGS, A. BAIRD *(Dept. of Biological Chemistry, Harvard Med. Sch. and the Res. Lab. of the Boston Lying-In Hosp., Boston):* Metabolism of C^{14} labeled glucose and pyruvate by rat diaphragm muscle in vitro. J. Biol. Chem. 195:287-97, March 1952.

The glucose and pyruvate utilization, glycogen synthesis, lactate accumulation, and metabolism of glucose and pyruvate to carbon dioxide by isolated rat diaphragm were measured in muscle from normal, diabetic, and adrenalectomized rats incubated in a phosphate-saline buffer containing labeled glucose and pyruvate. In all three types of animals, the addition of insulin increased glucose utilization, glycogen synthesis, and the amount of glucose metabolized to CO_2. The addition of insulin did not increase the total amount of pyruvate produced but did increase the amount of pyruvate made from glucose. The production of pyruvate from glucose as well as the utilization of pyruvate was found to be less in diabetic muscle than in normal or adrenalectomized muscle. The utilization was increased to normal by the addition of insulin. Insulin had no effect on pyruvate utilization in normal or adrenalectomized muscle.

The percentage of glycogen made from glucose was found to be increased and the percentage made from pyruvate decreased when insulin was added, but the actual amount of glycogen synthesized from pyruvate was unchanged by the addition of insulin. Although muscle from adrenalectomized rats synthesized less glycogen than normal muscle, a greater percentage of the glycogen formed came from glucose.

Confirmatory evidence, obtained by experiments in vitro, is presented that muscle has no glucose-6-phosphatase activity. No evidence for a glycerol-phosphorylating enzyme was found in muscle.

The authors believe that the experimental evidence is in accord with the theory that insulin produces a stimulation of the hexokinase system and that it has an additional effect on one or more of the reactions involved in the condensation of pyruvate with oxalacetate to enter the citric acid cycle.

VOLK, BRUNO W.; AND LAZARUS, SYDNEY S. *(Jewish Sanitarium and Hosp. for Chronic Diseases., Brooklyn, N. Y.):* Lymphocytic response of normal individuals to the insulin glucose tolerance test. Proc. Soc. Exper. Biol. & Med. 78:638-40, November 1951.

Absolute lymphocyte counts were performed in 12 normal individuals following insulin tolerance and insulin glucose tolerance tests. Since the change in absolute lymphocyte count after insulin plus glucose represented the summation of the effect of insulin and glucose given separately, the authors conclude that their data do not support the thesis that glucose after insulin magnifies the homeostatic response to hypoglycemia.

WAIFE, S. O.; WOHL, MICHAEL G.; AND SIGMOND, BARBARA *(Philadelphia Gen. Hosp., Philadelphia):* A correlation between changes in serum protein fractions in diabetes mellitus. Am. J. Med. 12:113-14, January 1952 [Abstr. of paper presented at the National Meeting of the American Federation for Clinical Research, held in Atlantic City, May 1, 1951].

The authors studied the relationship of serum albumin to serum globulin in diabetes mellitus. Statistical analyses were performed on 386 serum protein determinations (in duplicate) on 106 subjects (27 normal controls, 28 hospitalized diabetic patients, and 51 diabetics seen in the outpatient department). Albumin, globulin, and gamma globulin concentrations were determined chemically. Significant differences ($P<0.1$) were found in the mean value of total protein, albumin, globulin, and gamma globulin fractions of the three groups. The

hospitalized diabetics had a significantly lower albumin and higher globulin and gamma globulin than the controls. The clinic diabetics had intermediate values. The authors state that as serum levels fall in diabetes mellitus, definite and predictable rises in serum globulin, chiefly the gamma globulin, fractions occur.

WALLENFELS, K. The presence of free fructose in human blood. Naturwissenschaften, 38:238, May 1951.

By means of paper chromatography it has been proved that free fructose is a normal constituent of human blood in amounts ranging from 0.5 to 5 mg. per cent in normal individuals to higher quantities in cases of illness. Fructose is especially high in hepatitis and liver cirrhosis. It is usually high during pregnancy, especially before delivery, and injected levulose is assimilated to a greater extent during that time. Fructose is occasionally high in diabetic bloods.

WEBSTER, D. D.; AND BLADES, A. N. *(St. Luke's Hosp. and Central Clin. Lab., Middlesbrough, England):* Islet-cell tumor of the pancreas. Brit. M. J. 1:307-08, February 9, 1952.

A fatal case of functioning islet-cell tumor of the pancreas in a young woman is described. It is noted that symptoms were regularly associated with the start of the menstrual period. The pathological findings are reported, and some suggestions are made about treatment as with insulin coma therapy in schizophrenia.

WICK, ARNE N.; ALMEN, MARY C.; AND JOSEPH, LIONEL *(Scripps Metabolic Clin., La Jolla, Cal.):* The metabolism of sorbitol. J. Am. Pharm. A. (Scient. Ed.) 40:542-44, November 1951.

The total oxidation of C^{14}-labeled sorbitol over a twenty-four-hour period approaches that of labeled glucose when given to fed normal rats. Sorbitol administered orally is oxidized at a much slower rate for the first three hours. The slower rate of oxidation was shown to be due chiefly to delayed intestinal absorption. C^{14}-labeled sorbitol and glucose produce equal amounts of liver glycogen when given to fasted rats; the amount of incorporation of C^{14} in the glycogen is the same with the 2 compounds. It is believed that the metabolism of sorbitol proceeds through glucose.

WILDER, RUSSELL *(Bethesda, Md.):* Editorial: Diagnosis of diabetes mellitus. Am. J. Med. 12:1-2, January 1952.

The criteria of normality, value, and limitations of the one-dose standard glucose tolerance test in the diagnosis of diabetes mellitus are discussed. It is pointed out that data on the lactate and pyruvate levels of the blood obtained simultaneously with those on glucose in the glucose tolerance test may, in some cases, add to the value of the test. Pertinent literature is reviewed in regard to the influence of such factors as insulin, exercise, and glucose ingestion on the lactate and pyruvate levels of the blood both in normals and in diabetics. Recent studies on blood lactic and pyruvate acid in diabetes mellitus and in Cushing's syndrome are described. In those cases of Cushing's syndrome with frankly diabetic glucose tolerance curves the levels of pyruvate and lactate were very much above the levels attained in diabetes mellitus. In this respect, therefore, "steroid diabetes" was shown to differ strikingly from diabetes mellitus.

ZILVERSMIT, D. B.; AND DILUZIO *(Div. of Physiology, Univ. of Tennessee, Memphis):* Synthesis of phospholipides in diabetic dogs. J. Biol. Chem. 194:673-83 February 1952.

With the aid of P^{32}, phospholipid synthesis in the liver, kidney, small intestine, muscle, and brain was compared in 10 depancreatized and 15 control dogs. In the diabetic dogs, marked increases in phospholipid synthesis were found in liver and plasma. Slightly smaller increases of phospholipid synthesis were also observed in small intestine and kidney. In skeletal muscle there was a questionable increase in phospholipid synthesis, and the rates of synthesis of brain phospholipid in diabetic and control animals were found to be identical. Evidence is presented which the authors believe is compatible with the hypothesis that phospholipids are intermediates in fat oxidation.

ZUCKER, GARY; AND MARDER, MAXWELL J. *(Med. Serv., Beth Israel Hosp., New York City):* Charcot spine due to diabetic neuropathy. Am. J. Med. 12:118-24, January 1952.

A case of Charcot spine due to diabetic neuropathy is described. The diabetic etiology was substantiated by complete pathologic examination. The authors believe that this is the first such case recorded in the literature.

EDITORIALS

HEREDITY IN DIABETES

Two recent studies, one by Thompson and Watson[1] in this issue of DIABETES, the other by Steinberg and Wilder[2] in the June issue of *American Journal of Human Genetics,* lend support to the conclusion of Pincus and White[3] that predisposition to diabetes, in the great majority of pedigrees, is a simple Mendelian recessive.

The Thompson and Watson data were obtained in London, Ontario, in a study of 1631 diabetics, their parents, sibs and offspring. The data of Steinberg and Wilder were obtained at the Mayo Clinic from a consecutive series of 1981 "new" diabetic patients, i.e., patients who previously had not visited the Clinic with detectable diabetes.

Both of these sets of data, like the data earlier reported by Harris,[4] disclose a tendency for the diabetic sibs of diabetic patients to become diabetic at the same age as the patients. This, however, as is pointed out in both of the reports, may be a statistical rather than a biological phenomenon. Neither of these newer studies reveals significant association between the sex of the patient and that of his diabetic parent or sib, failing in this to confirm the earlier data of Penrose and Watson[5] which suggested such association.

The data of Steinberg and Wilder, as analyzed by them, prompted additional interpretations, as follows: 1. The average age of diabetics is unaffected by the sex of the patient. 2. The average age at onset is unaffected by the existence of diabetes in the parents of the patients. It was 47, 48 and 45 years respectively when none, one, or both parents were diabetic. 3. The birth order of the patient is without significance.

In contrast with what might be suspected, these data (as well as those of Pincus and White and of Harris) reveal a slightly greater average family size when diabetes occurs in one or even in both of the parents. The data, however, as is emphasized, relate only to those matings which have yielded at least one diabetic child.

The details of the genetic analysis by Steinberg and Wilder of their data and the data of others, including investigators who had proposed other hypotheses, cannot be presented here. They support the view, as has been said, that predisposition to diabetes is inherited as a Mendelian recessive character. This means that if d represents the condition of the gene which leads to a susceptibility to diabetes and D its normally functioning alternative condition, diabetics and potential diabetics are genetically dd and those not genetically liable to diabetes are either DD or Dd. The partners of *matings which yield diabetic offspring* may both be nondiabetic

(genetically such a mating is Dd x Dd) or one partner may be diabetic and the other nondiabetic (genetically the mating is dd x Dd) or both partners may be diabetic (genetically the mating is dd x dd). The relative frequency of diabetic offspring from these three types of matings (assuming essentially the same age distribution for the three sets of offspring) is as 1:2:4. The absolute values will depend on the age distribution of the sample; however, on the average *one-quarter* of the sibs of a diabetic patient with *nondiabetic parents* will be genetically predisposed to diabetes; on the average *one-half* the sibs of a diabetic patient with *one diabetic and one nondiabetic parent* will be genetically predisposed, and *all* offspring of matings in which *both parents are diabetic* will be predisposed to diabetes.

The knowledge that all of the offspring of a mating of two diabetics inherit the predisposition to diabetes is of great importance. If all such persons must develop diabetes, given time, they provide the material needed for studies of the prediabetic state. Also, diabetics obviously ought never to marry diabetics. It would be even safer, if they marry, to choose as mates the offspring of persons who are not the children of diabetics.

Steinberg and Wilder, by genetic analysis of their data, arrive at estimates of the prevalence of diabetes and prediabetes. They conclude that diagnosed diabetics constitute about one per cent of the population of the United States, a conclusion in close agreement with those of others, based on surveys. They estimate that those who are genetically dd, that is, the diagnosed, undetected and potential diabetics, approximate five per cent of the population. As the average age of the population increases more prediabetics will have time to manifest their diabetes, and so the prevalence of frank diabetes must continue to increase as undoubtedly it has increased in the last few decades. Here is a challenge to preventive medicine of more significance even than detection of the undiscovered diabetic.

—RUSSELL M. WILDER, M.D.

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3 Pincus, Gregory, and White, Priscilla. On the inheritance of diabetes mellitus: An analysis of 675 family histories. Am. J. M. Sc. *186*:1-14, 1933.

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5 Penrose, L. S., and Watson, E. M. A sex-linked tendency in familial diabetes. Proc. Am. Diabetes A. 5:163-77, 1945.

FINANCIAL SUPPORT OF RESEARCH

A recent issue of *Science*[1] contained a detailed report on the financial support of medical research in the United States during the past six years. Many readers of DIABETES will be interested in certain data contained in the report, and also in information concerning the organization responsible for its preparation.

The Medical Sciences Information Exchange is a cooperative endeavor established in July 1950 within the Division of Medical Sciences of the National Research Council. It is jointly supported by six agencies of the federal government—the Army, the Navy, the Air Force, the Atomic Energy Commission, the Public Health Service, and the Veterans Administration. They maintain it as a clearing house for information on grant and contract support in the medical and allied fields. It compiles data concerning awards for research made by foundations, industries and others, in addition to the government. It is reported that investigators throughout the country, as well as granting agencies, make daily use of the Exchange, an indication of its success in meeting a definite need.

In the report, an analysis was presented of 12,923 research grants registered with the Medical Sciences Information Exchange during the period 1946 through 1951. In these six years $135,044,125 was awarded, $83,110,671, or 61.5 per cent, from government and $51,933,454, or 38.5 per cent, from private sources. The annual funds increased from 4 million dollars in 1946 to 33 million in 1949, and have remained at approximately this level. Government support, 44 per cent in 1946, has steadily increased until in 1951 it provided nearly 66 per cent of the total support of medical research. Funds from private sources increased from 2 million in 1946 to 11 million in 1951; apparently increasing government support of medical research has not diminished the efforts of the private foundations.

Of special interest is the information concerning re-

TABLE 1 Expenditures for research in diabetes

Year	Government	Private	Total
1946	$ 0	$ 6,700	$ 6,700
1947	25,580	24,800	50,380
1948	141,908	45,411	187,319
1949	242,622	54,841	297,463
1950	309,985	70,771	380,756
1951	353,544	74,505	428,049
1946-1951	$ 1,073,639	$277,028	$1,350,667

search on diabetes (see Table 1). The total expenditures recorded for the six-year period were over $1,350,000, four-fifths from the government and one-fifth from private sources. It is of even greater significance to note the rapid increase in the attention given diabetes in this short period. In 1946 the expenditure of only $6,700 was recorded; all of this came from private funds. In 1951 the sum from private funds had increased eleven-fold, approaching $75,000; in the same year government support, which began in 1947, climbed beyond $350,000.

It is apparent that fundamental research bearing ultimately on diabetes may not be classified under this heading. Attention should therefore be directed also to the total sums spent in the general fields relating to diabetes. For metabolism and nutrition the expenditure was $7,681,603 in the six-year period; 55 per cent was provided by the government. For the endocrine system the amount was $3,056,095, 75 per cent provided by the government.

A full appraisal of the results of the research activities made possible by these expenditures has not yet been attempted, and indeed is scarcely possible. However, one immediate result is already apparent, namely, the increase in the number of publications reporting investigations, and the establishment of new journals. An important by-product is the training of young investigators who are given the opportunity to develop interests and skills, which should yield dividends soon.

The present report will be viewed with a variety of feelings. Some will feel that nothing but good is indicated by these expenditures for medical research. Others will deplore the dominance of expenditures by the government. Still others will be conscious of the fact that expenditure alone is not an index of achievement. All will agree that even with increased financial support, progress in research will continue to depend on even more important factors—genius, inspiration, and work.

REFERENCE

[1] Deignan, Stella Leche, and Miller, Esther. The support of research in medical and allied fields for the period 1946 through 1951. Science *115*:321-43, March 28, 1952.

PAST, PRESENT AND FUTURE

The annual meeting of the American Diabetes Association in June marked the conclusion of the twelfth year of its existence. During these dozen years, substantial achievements have been made, as outlined in the address of the retiring President, Dr. Arthur R. Colwell. Not the least of these has been the thorough appraisal of the purposes and policies of the Association, conducted under his leadership. The report of his Committee, presented in the first issue of DIABETES, will help to guide our present and future plans.

The meeting itself was highly successful from the standpoint of both attendance and program. The scientific papers were suitably diversified as to subject, and reached a high standard of quality. Many of them have been scheduled for publication in DIABETES, some appearing in this issue. An outstanding event was the delivery of the Banting Memorial Lecture on "Insulin" by Professor Charles H. Best.

The thirteenth year of this Association presents a new opportunity both to maintain and develop activities now in progress and to initiate new projects by which to achieve more fully the Association's objectives. Among the latter, two deserve mention at this time. One is the presentation of a post graduate course for advanced training of physicians in diabetes and related physiological problems; this is scheduled for January 19, 20 and 21 in Toronto. A second is the offer of a prize for the best paper on diabetes written by a student or intern, announced on page 338 of this issue.

The Journal, started in the current year, is still our newest venture of major importance. In this early stage of its existence, members of the Association are invited to submit constructive criticisms. Contributions will also be welcomed by the Editorial Board.

Suggestions and comments are also invited in regard to other phases of the Association's activities. Let us all work together to make this thirteenth year of the Association a year of good fortune and continued progress.

FRANK N. ALLAN, M.D.
President
American Diabetes Association

Remarks upon the Presentation of an Award to

Charles H. Best, M. D.

By the American Diabetes Association

Elliott P. Joslin, M.D.

BOSTON
HONORARY PRESIDENT
AMERICAN DIABETES ASSOCIATION

Upon the festal occasion of this Twelfth Annual Meeting of our Association a brief interlude has been reserved for a matter of especially happy import; and I would like to solemnize it by quoting the words of introduction to a will in which a large portion of the testator's fortune was given to diabetes:

IN THE NAME OF GOD, AMEN

The matter to be discussed at this time is the presentation of an award to one Charles H. Best, born of Canadian parents in the United States in 1899 and now a resident of Toronto, Ontario, Canada.

Dr. Best: In searching your background for reasons for your achievements, I have found that they are too many and that some of them arose from circumstances not exactly under your control.

For example, your father was a country doctor, and he brought up his son in a medical atmosphere of service to those about him such as exists only for a general practitioner in a rural community. Your mother, too, was an ideal country doctor's wife. She also came from the Annapolis Valley in the Evangeline country of Nova Scotia, and I am told that she was so filled with the spirit of hospitality that seldom did anyone, friend or stranger, leave her door without bearing a gift of food or flowers. She was always doing something for someone else.

Then there was your aunt, Miss Best, whom I knew so well in house officer days at the Massachusetts General Hospital in 1895, when she was a nurse in training. Despite the frugal recompense nurses then received, she saved her money —a wholesome but now too often outmoded trait—and from your own lips I learned that she helped your father through medical school. Later she developed diabetes, finally diabetic coma; and I know how sad I was that I could do nothing for her. The impact of her life—and death—turned your thoughts toward diabetes. I remember that several years after insulin was discovered, when I heard you speak in Philadelphia, I noticed you took from your vest pocket a woman's watch. It was your aunt's, Miss Best's.

Finally, credit must be given to a girl who, with the instinct for quality inherent in the best of womankind, divined possibilities in you when you were an unknown.

Remember? You were working your way through medicine by hard physical work in the summers because that was so much more remunerative than a white-collar job. This girl met you, and then and there gave you her heart.

Dr. Best: tonight this emblem is being given to you not for what you have done; not, for example, for your share in the discovery of insulin with Banting. That is all in the past, and your role in that immortal discovery is secure. Thucydides put it well when he recorded the speech of Pericles in honor of the heroes of the first Peloponnesian War, and said of them: " . . . For they received again each one for himself a praise which grows not old . . . There dwells also an unwritten memorial of them, graven not on stone but in the hearts of men."

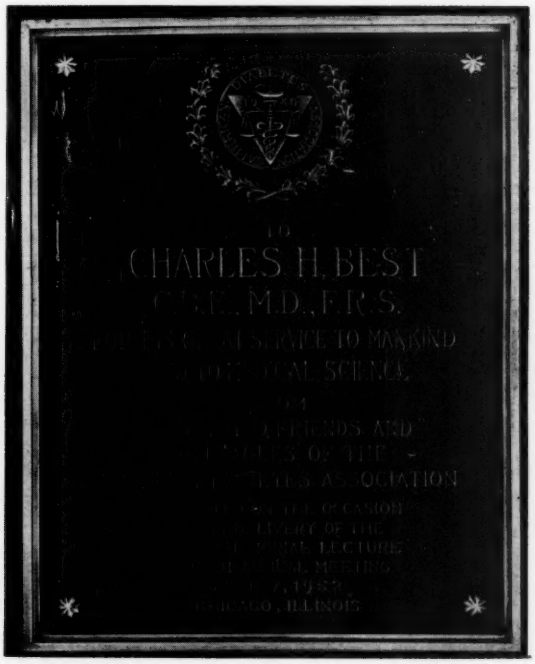
Nor do we give this tribute to you out of love and affection. We would enjoy doing that, of course, although I venture the thought that we would prefer to extend such a symbol to your better half.

Professor Best, this token is not in recognition of your present activities as an educator, because that recognition you have already received. Indeed, just as Henry Christian once said of Otto Folin that there was no hour in the day but what some laboratory somewhere in the world was utilizing his chemical methods, so with you there is not a moment in the 1,440 minutes of the twenty-four hours but what some student or physician somewhere is studying your book and your latest scientific papers for instruction and inspiration.

Since it is not for your discoveries in the past, not for love, and not for your present teaching activities that I conceive that the members of the American Diabetes Association have assembled to confer this award upon you, the question must be asked: Why have we? What are our motives in thus presenting to you the highest distinction in our power?

This plaque is bestowed upon you, Dr. Best, because of our belief in your future. Despite achievement after achievement, you have never stopped working, you have never ceased broadening your interests or your responsibilities. Once you traveled to spread a knowledge of diabetes control and thus to save the lives of hundreds of thousands of diabetics. Now you journey to investigate other diseases, and to learn how to banish them from the world and thus save millions upon millions of lives.

PROF. BEST (L.) RECEIVING PLAQUE FROM DR. JOSLIN



TEXT OF THE PLAQUE PRESENTED TO PROF. BEST

We give you this award, too, because we know that you sense the necessity for raising the social along with the medical status of the backward, the impoverished, the ignorant and sick, so that they also can share in the health and happiness and safety which we enjoy. We present you this token from your friends because of our confidence in your expanding future, knowing that now you have acquired a platform from which you can speak with authority, a pulpit from which what you say will be carried to the whole civilized world.

May you continue to have health to begin the second half of your life "for which the first was made." May you never cease enjoying your hard work, your added duties, your new opportunities. May you continue to be a roving ambassador for health, peace and plenty for all people.

Like Longfellow, you were born in Maine. Hence it is not inappropriate to repeat, in closing, the familiar lines of your State's laureate:

"Sail on, nor fear to breast the sea!
Our hearts, our hopes, are all with thee,
Our hearts, our hopes, our prayers, our tears,
Our faith triumphant o'er our fears,
Are all with thee,—are all with thee!"

The Award of the Banting Medal to Professor Robert Russell Bensley

AT THE TWELFTH ANNUAL MEETING
AMERICAN DIABETES ASSOCIATION
CHICAGO, JUNE 7, 1952

PRESENTATION BY

Arthur R. Colwell, M.D.

CHICAGO

PRESIDENT, AMERICAN DIABETES ASSOCIATION
1951—1952

It is our privilege to pay tribute to a great scientist, Robert Russell Bensley, who is now Professor Emeritus of Anatomy at the University of Chicago.

Born eighty-four years ago in Hamilton, Ontario, Dr. Bensley received his college and medical training at the University of Toronto, served there on the biological faculty for ten years and then, in 1901, came to the University of Chicago in the Department of Anatomy. He has been there ever since, a celebrated teacher and investigator. Theoretically retired in 1933, he continued his studies as a biologist, chemist and pathologist at an even more accelerated pace than before.

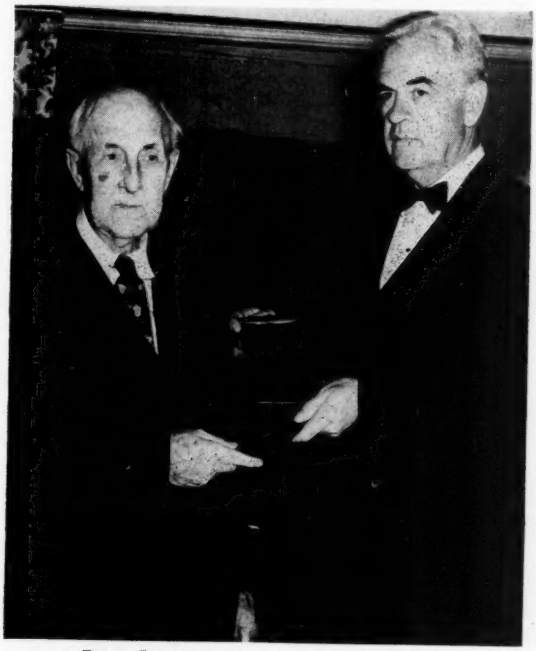
Dr. Bensley's accomplishments should require no recounting for this audience. He is best known for the fact that early in this century he and his students firmly established the existence of the islets of Langerhans as separate in structure and function from the acinar cells of the pancreas. The individual characteristics of the

alpha and beta cells were clearly defined by supravital staining methods.

Not so well known but possibly even more important are his discovery of the neck chief cells of the gastric mucosa, the studies on the secretory function of the cells of the duodenal glands of Brunner and on the mechanism of hydrochloric acid secretion in the stomach, the demonstration of the secretion antecedent in the cells of the thyroid gland, and his early establishment of the identity of the Golgi apparatus of animal cells. His original fixing and staining techniques have led to important revelations of the chemical and structural composition of cell protoplasm, both in his own hands and in the hands of some of his well-known students, particularly Arnold Lazarow, Normand Hoerr, Isidore Gersh, and E. V. Cowdry. It seems characteristic of Dr. Bensley that his contributions after retirement, presenting new concepts of the structure of the cell, its chemical composition and its functioning, are acknowledged to be the most significant of his entire career. Cowdry pays him high tribute for great generosity with his ideas, the characteristic of pushing others forward but never himself, his wide knowledge of nature, and credits him with being a dynamic experimentalist and founder of the new cytology.

Dr. Bensley has said, "It does not matter *who* is *right;* the only important question is, *what* is *true?*." This simple but profound observation undoubtedly expresses in a few words his chief scientific philosophy. It explains why he has accomplished so much, why those accomplishments have grown in stature with the passage of time, and why those who know him well are so devoted to him.

Robert Russell Bensley, it is my privilege as representative of the American Diabetes Association to give you another honor, in addition to the many which have already been bestowed upon you. The Banting Medal is presented by this Association only to those who have rendered great service in the field of diabetes. You have certainly done so, and we are glad to be able to acknowledge it in this way.



PROF. BENSLEY (L.) AS HE RECEIVED THE BANTING MEDAL FROM DR. COLWELL

BOOK REVIEWS

DIABETIC MANUAL, FOR THE DOCTOR AND PATIENT. *By Elliott P. Joslin, M.D., Clinical Professor of Medicine Emeritus, Harvard Medical School, and Medical Director, George F. Baker Clinic, New England Deaconess Hospital, Boston, Massachusetts. Eighth edition. Cloth. $2.50. Pp. 260. Illustrated. Lea & Febiger, Philadelphia, 1948.*

A PRIMER FOR DIABETIC PATIENTS. *An Outline of Treatment for Diabetes with Diet and Insulin, Including Directions and Charts for the Use of Physicians in Planning Diet Prescriptions. By Russell M. Wilder, M.D., Formerly Professor and Chief of the Department of Medicine of the Mayo Foundation, University of Minnesota, Senior Consultant in the Division of Medicine, Mayo Clinic; now Director, Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland. Ninth edition. Cloth. $2.50. Pp. 200. Illustrated. W. B. Saunders Co., Philadelphia, 1950.*

YOUR DIABETES: A COMPLETE MANUAL FOR PATIENTS. *By Herbert Pollack, M.D., Associate Physician for Metabolic Diseases, Mount Sinai Hospital, New York; and Marie B. Krause, M. S., Consulting Dietitian. Second edition. Cloth. $3.00. Pp. 212. Paul B. Hoeber, Inc., New York 16, 1951.*

DIABETES CONTROL. *By Edward L. Bortz, M. D., Chief of Medical Service B., Lankenau Hospital, Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Cloth. $3.50. Pp. 264. Lea & Febiger, Philaadelphia.*

LEITFADEN FUR ZUCKERKRANKE. *von Dr. Med. Georg R. Constam, Zurich, Switzerland. Second edition. Cloth. Leinen Fr. $12.50. Pp. 114. Illustrated. Benno Schwabe & Co., Basel, Switzerland, 1951.*

Books about diabetes written for the instruction of diabetic patients have come to play an important part in the management of the disorder. They furnish effective instruction to physicians as well as laymen. That they fill a need is indicated by the appearance of a growing number of such books on the market, and by the publication of repeated editions of those which have been most successful. Five of these books, introduced or reprinted in the past year or two, are reviewed herewith.

Joslin's "Diabetic Manual" seems to have been the first in the field. It appeared in May 1918. Its popularity is shown by the fact that it reached its eighth re-editing in 1948 and has been reprinted in each succeeding years. It contains information regarding the various problems of the diabetic. It also contains in each of its thirty chapters something of the stimulating personality of its author. In simple, direct language he makes clear what the diabetic should know. By recounting illustrative experiences of his patients, and by apt quotations from the poets, from the bible and other sources, he makes it easier for the reader to remember his points. He stresses not only diet and insulin but "the art of learning how to get the most out of life under all circumstances."

The "Primer" by Wilder, first published in 1921 and now appearing in its ninth edition, also has the reputation of seasoned experience. It is practical; the nature of the metabolic disorder is discussed briefly, but most of the text consists of straightforward directions concerning the procedures which the patient must learn regarding tests, insulin, diet and hygiene. More than half the book is devoted to diet, including recipes.

The books by Pollack and Bortz are recent. Both employ the food values and the system of food exchanges contained in the American Diabetes Association's "Diabetes Guide Book for the Physician." On this basis, the authors present an elaboration of the dietary program which should simplify this phase of treatment for the patient and prepare him for any situation.

The first chapter of Pollack's "Your Diabetes" is entitled "You Can Live A Normal Life." The optimistic introduction is supported by stories of diabetics who have had successful careers. The nature of diabetes and the researches which have led to progress are presented in readable fashion. Finally, the details of treatment are explained fully.

"Diabetes Control" by Bortz likewise provides inspiration and encouragement to the diabetic reader. It emphasizes particularly the psychological aspects of the management of diabetes. It contains information regard-

ing the detection of diabetes in the population. It discusses life insurance, longevity, retirement, and other matters outside the ordinary range of medical treatment.

Constam's book is concise but complete. It follows the teaching common to the other books. It should be extremely valuable for those who seek instruction in the German language.

Each book has its special merits and each one of them can be recommended as an aid to the physician who seeks help in the instruction of his patients. It would be desirable for physicians to make them all available for his patients permitting the patient himself to choose which one he will wish to purchase and keep available in his own home for ready reference.

CURRENT THERAPY 1952. *Edited by Howard F. Conn, M.D.* $11.00. *Pp.* 849+xxxi. *W. B. Saunders Co., Philadelphia,* 1952.

In these days of rapid advances in therapy a book of this kind published annually is in order. Both the editor and the contributors are men of ability and excellent reputation. The manner of presentation of the material is unique in that treatment methods of individual experts have been selected by the contributors without comment. In the average textbook the author usually discusses the treatment he himself has adopted and may comment on other methods. The new system is simpler and probably quite adequate.

The book appears to give rather complete coverage. One may note with interest that under the treatment of diabetes mellitus several different methods are presented. Dietotherapy for diabetes is usually made too complicated, and also is made to appear to be as exact as mathematics; nevertheless the two main methods given in this volume contain very different figures. The one by Duncan appears to have excessively high protein content.

In general, one finds little in this book that would require adverse criticism. It can be recommended highly for the busy practitioner.

CORRESPONDENCE

TO THE EDITOR:

The paper entitled "Pituitary Necrosis in a Diabetic During Pregnancy," by Dr. Frederick W. Williams, published in the January-February issue of DIABETES, brings to mind a case treated at the Boston Lying-in Hospital which presented a similar phenomenon, but with recovery.

A 19-year-old primigravid patient who had diabetes of one and a half year's duration was seen during the seventh week of pregnancy and was followed from that time onward. She had been taking 40 units of protamine zinc insulin and 10 units of crystalline insulin daily.

She was one of the first cases in which blood and urine estrogens were studied by the Smiths. These tests were abnormal, indicating impending toxemia. She developed edema of the face at the thirty-fourth week of pregnancy. One week later she had a generalized convulsion and was admitted to the hospital with an elevated blood pressure and albuminuria graded 4 plus. During the first 24 hours she had several convulsions. Two days after the onset of convulsions, labor started and she was delivered of a normal baby of 8 pounds 3½ ounces.

In the convulsion occurring the day after admission, the blood sugar was 40; the blood pressure at this time was 195/112. She was given glucose intravenously during the convulsion, and it ceased immediately; she awakened and was rational. The insulin dosage was reduced sharply; and finally, because of recurring convulsions, was omitted. She required no insulin for 13 days. Blood sugar tests at this time were reported 103, later going up to 188. Finally treatment with insulin was resumed on the thirteenth day. She was eventually discharged on a dosage of 54 units of protamine zinc insulin and 16 units of regular insulin.

During this time she had a combined glucose-insulin tolerance test (100 gm. of glucose given orally, 5.5 units of insulin given intravenously). It was reported as follows: Initial blood sugar, 92; in 20 minutes, 102; in 30 minutes, 108; in 45 minutes, 135; 1 hour, 145; 2 hours, 123; 3 hours, 126.

At the time, this case was considered to be one in which pre-existing diabetes was improved by damage to the anterior pituitary gland, which is well known to occur in eclampsia. In this case, the damage was temporary and reversible, since she again required insulin in the usual dosage.

DAVID HURWITZ
Consultant in Diabetes
Boston Lying-in Hospital

ORGANIZATION SECTION

Past Accomplishments and Future Needs

PRESIDENTIAL ADDRESS
DELIVERED AT THE ANNUAL BANQUET, JUNE 7, 1952
TWELFTH ANNUAL MEETING, AMERICAN DIABETES ASSOCIATION
CHICAGO, ILLINOIS

Arthur R. Colwell, M.D.

IRVING S. CUTTER PROFESSOR AND
CHAIRMAN OF THE DEPARTMENT OF MEDICINE
NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO

It has been a rare and satisfying privilege to serve the American Diabetes Association during some if its years of lusty growth. While being indoctrinated on its Council and in committee meetings, I became increasingly aware of the qualities of this organization that keep many people from all over the country active in its work, tolerant of its faults, and ambitious for the future. But only as presiding officer have I been able really to appreciate the full power of this Association.

In a dozen years of growth and development we have done many fine things. As a prelude to my chief message to the membership of this Association tonight I want to acknowledge some of them. I know that it is hazardous to dare to mention some things and omit others, and even more so to try to name individuals responsible for them. Please forgive me if I do this ineptly. Yet certain high points in our career and specific people to be thanked for them stand out in my mind, and I propose to name names, dates and person, with as much judgment, I hope, as presumption.

Few will deny the virility of those who conceived this organization and delivered it by expert midwifery from the fertile womb of American diabetic interests. This was an act of love and tenderness, due for the most part to the imagination and devotion of three elder statesmen who will appear a little later on this program. Their wisdom is attested by the steady, healthy growth of their offspring, and by the sponsors, preceptors and followers it has attracted in its career.

Second in importance only to our birth is the rapid rate of our development in many directions. We took a long leap forward in our good work when we began to publish the *Forecast* five years ago. This little magazine for the patient has done a great deal to spread authoritative and useful information about diabetes. Without advertising, it now pays its way with a circulation of more than twenty thousand, and it is growing steadily. Dr. Edward Dillon of Philadelphia deserves most of the credit for getting this project launched. For its record during the last two or three years we salute Dr. Frederick Williams of New York, its present editor. He has improved its interest and style, with little help from others outside of the National Office, and is passionately devoted to its cause.

We are probably best known in the professional and public minds for our crusade to discover unknown diabetes and to promote good medical care for known diabetics. The detection campaign was primarily the idea of Dr. Howard Root of Boston, who managed the

first two drives. Dr. John A. Reed of Washington has succeeded to this throne. The size and scope of the project, as well as its acceptability from the professional relations standpoint, are eloquent testimony to the taste and judgment of Root and Reed, the detection partners. After an initial phase of skepticism about the value of this work, I am now fully convinced that it is one of the most important things we do. Recognition of diabetes and stimulation of diabetics to take care of themselves are only part of the accomplishments of this campaign. Authoritative public knowledge about diabetes is an equally important, though indirect, additional result of those efforts.

Performances are generally much more impressive if they can be accompanied by an element of sentiment and pageantry. It is not generally known, but I believe Dr. Joseph Barach is long overdue for a substantial vote of thanks for originating and staging such unforgettable events as our Toronto meeting celebrating the twenty-fifth anniversary of insulin, the annual Banting Memorial lectures, and the Banting Medal presentations.

Our scientific publications long have been the work of two men, Dr. Frank Allan of Boston and Dr. Franklin B. Peck of Indianapolis. In addition to their editorial work on the annual Proceedings, Dr. Allan had a major role in the preparation of our Guidebook for Physicians and Dr. Peck in the publication of our Abstracts. During the current year they have sent our new scientific journal off to an auspicious start. Dr. Allan, as editor, has carried the major share of this new load.

In most of these enterprises J. Richard Connelly has been the hard working man behind the scenes. My list of acknowledgments would be thoughtless if I failed to pay particular tribute to his foresight and skill in consolidating our business and editorial offices; rallying a fine, loyal office staff around him; perfecting our accounting system; promoting our publications; putting the Association on an acceptable business basis in all respects; and gaining the complete confidence of our family of physicians, all in the space of three years. Some of us had expected that the enlistment of his services would leave little work for the officers and directors to do. His talents are further shown, however, by the fact that he knows that our interest is best maintained if we are kept at work. Therefore, for every administrative job he has removed, he has created several new and different ones.

I presume that every president retires from office with parallel emotions of relief and regret. The relief that comes with shedding of responsibility is strongly colored by the sobering realization that much more could have been accomplished, and sorrow that it was not. Likewise, every retiring president who has deserved his office is in a strategic position to define what those missing feats could have been and how they might be accomplished in the future. The skipper of a ship quickly learns what it can do and how, and what it cannot do and why. On the eve of retirement I should like to call your attention to what I consider to be our greatest need at present, together with a few hints as to how it might be supplied.

Approximately one person in each one hundred is diabetic. Likewise, about one American doctor in one hundred is sufficiently interested in our purposes to belong to and support this organization. In contrast to similar associations in other countries, we have not encouraged nonprofessional *active* membership or control in the national association. I believe that as long as physicians remain devoted to our cause it will be wise not to change this policy. Just as the dependable and well-informed physician knows best what is good for the individual diabetic patient, so does a group of physicians know what is best for them all. If we should weaken in our judgment or in our zeal to promote what is best, then it will be time to contemplate a change to nonprofessional management. Until then, however, (and I hope that time will never come), physicians can guide our national course most wisely.

On the other hand, systematic participation in appropriate activities by the interested public should be expanded. Some thirty local associations have been organized, largely due to the crusading of our former secretary, Dr. George Anderson of Brooklyn. Most of them are active and are working hard in their own areas to help do good for diabetics. But a country composed of many states and large cities eventually should have a hundred or possibly several hundred such local groups. More important, since all of them will aim at the same objectives, which are also our own, they should have guidance, not only in their formation, but also in program development after they are formed, from each other and from national headquarters. I visualize this as our greatest need at the present time.

Recently we have been given an invaluable assist toward this goal in the form of money to subsidize a field program. A full-time travelling representative has been employed. For two months he has been learning of our work in the National Office. Soon he will take to the road to learn more about the strengths and weaknesses of our existing affiliates and the opportunities for the formation of others. When this picture is

assembled it is hoped that we will be resourceful enough to plan what is to be done and how to do it.

It would be ambitious of anyone to try to solve this problem without at least that much study and understanding. Yet, pending the results of a survey like that contemplated, certain general principles can be defined. Indeed, it may be easier to do this before too much detailed information is at hand for fear of not being able to see the forest because of the trees. After all, our general purposes have stood the test of time exceedingly well, even though we have devised many methods of attainment.

All will agree that a well-informed national group should inspire and coordinate local efforts. As stated previously, I hope that this group will continue to be composed of dependable and interested physicians who have the same missionary spirit that is our greatest asset so far. It seems obvious that it would not be feasible to create an active national membership of working lay people, no matter how interested they might be. As a homogeneous society they simply could not serve or be served on a country-wide basis because of the distances and mechanical problems involved.

Therefore it seems rational to continue the formation of local societies, to assist in their work towards a common goal by providing inspiration and strength if they falter, diagnosis and treatment of faults if these exist, recognition of constructive ideas and methods as they appear, with wide dissemination of the best of them for the benefit of others who can use them to advantage. Such integration and guidance can come only from national headquarters, and any national group which fails to provide them will remain a small, impotent academy, and will be replaced by one which does.

Granting, then that a national, guiding, professional organization and many sectional societies containing laymen should coexist, what should be the relationship between them? At the present time this is limited to encouragement of formation of local societies, their recognition by approval and charter, exchange of information by mail via the *Forecast,* and promotion of education about diabetes and its early discovery, also largely by mail through the activities of the Detection Committee. The loosest kind of organizational relationship exists, in which the national body gives and the local society receives, for the most part. This is as it should be, for the present.

As affiliates grow in number and strength, however, they should support the parent which nourished them. It seems to me that organizational procedure, logically, should consist of three levels of related associations, each with its own function and membership. To some extent membership would be interlocking. First, there should be a national physicians' group, as at present, which recognizes, guides and directs local societies on the most appropriate geographical basis. Next, there should be many local societies of physicians, all of whom are automatically also members of the American Association and receive our journal. They, in turn, should organize and guide the activities of lay groups in their areas. These should make up the third level. Their members automatically should be adjunct members of the American Association and receive our lay journal as a condition of their membership.

It is recognized that these three organizational levels now exist in an informal, heterogeneous fashion. Their patterns and relationships to each other have not been defined, however. We seem to have accumulated the

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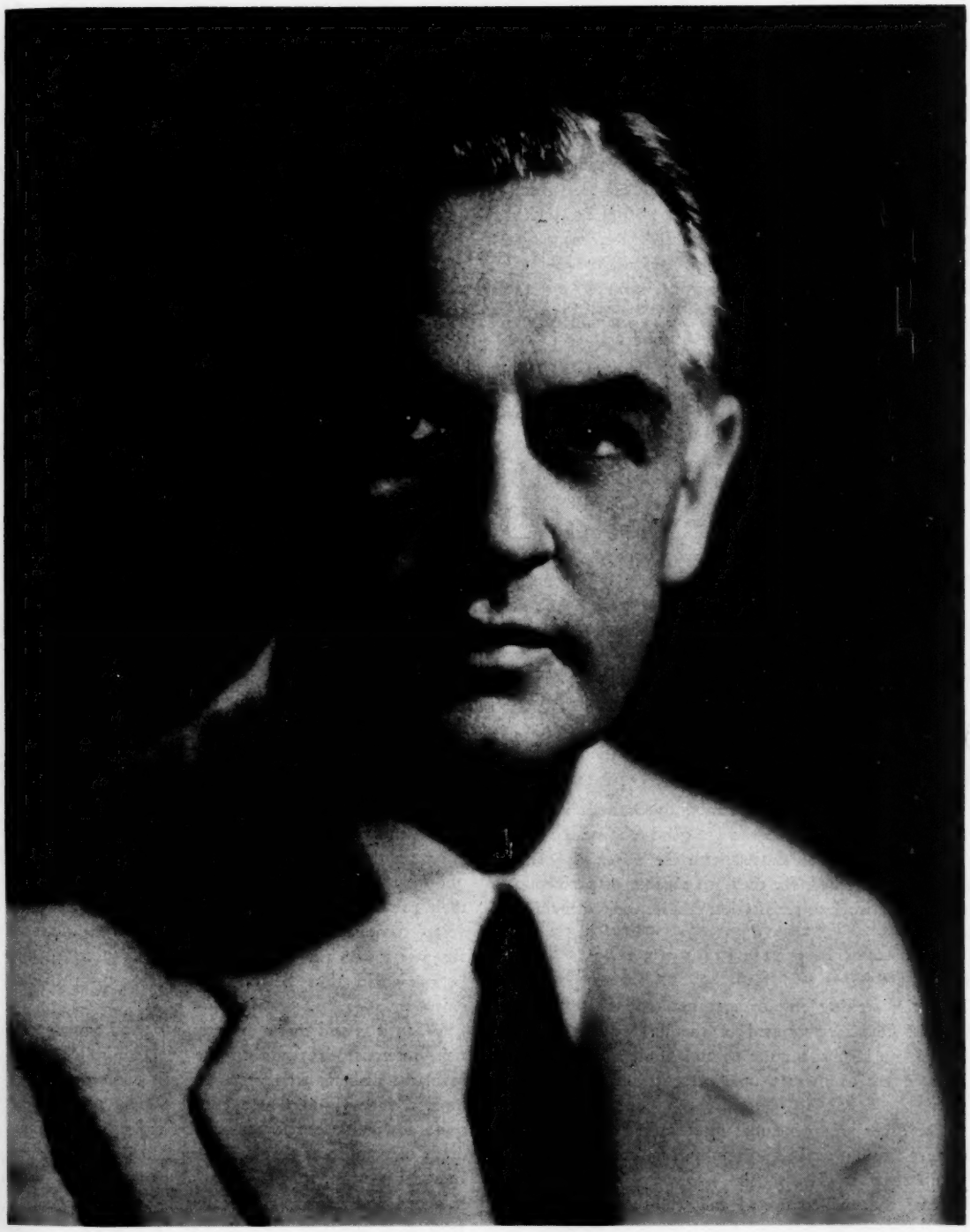
ARTHUR R. COLWELL

Dr. Colwell's term as President followed many years of important service to the Association as officer, councilor and committee chairman. He was one of the founders and a past president of the Chicago Diabetes Association.

He attended the University of Chicago, receiving the degree of S.B. in 1919, and Rush Medical College, graduating in 1921. He was intern in the Presbyterian Hospital, Chicago, 1922-23. Then he went to Harvard Medical School, 1928-29, as Fellow in Medical Research of the National Research Council. He is a member of Alpha Omega and Sigma Xi.

A member of the faculty of Rush Medical College from 1923-33, he has been on the faculty of Northwestern University Medical School since 1933. In 1950, he became chairman of the Department of Medicine and Irving S. Cutler Professor of Medicine. He is the first full-time Professor of Medicine at Northwestern University and is also chairman of the Division of Medicine of Passavant Memorial Hospital in Chicago.

Dr. Colwell is the author of two books on diabetes and of many papers dealing with research and practice in the field.



materials for a strong structure but have failed to tie them up neatly into a form in which they can support and give strength to each other.

In order to accomplish this type of organization several specific problems require detailed solution. For example, constitutional revisions of both national and local bylaws would be required, all on a uniform basis. Adjustments in dues and subscription rates should be planned so they would not be harmful to local memberships. Geographical responsibility should be defined on a feasible basis and standardized. Representation should be arranged for lay groups on local professional boards, and for local professional groups on the national board.

I am convinced that we have reached a stage in our development where thoughtfulness and hard work toward organizational objectives similar to these is now required. If we fail to recognize the need or to meet it if we see it, we shall stop growing stronger and may even relapse. Now that the American Diabetes Association can review with pride its birth, growth, regional expansion, public education and detection activities, fine popular and scientific journals, improvement in scientific meetings and exhibits, establishment of a business-like national office, and above all, retention of the almost fanatic missionary spirit which has made all these things possible—now that we can look back with pride on these things and others, we should look ahead organizationally and strengthen our position and that of our affiliates. When this has been wisely accomplished we can begin to do more towards realization of our other great need, full support of research.

Employment of Diabetics

STATEMENT OF THE COMMITTEE ON EMPLOYMENT AMERICAN DIABETES ASSOCIATION JULY, 1952

It is the philosophy of the American Diabetes Association that controlled diabetics are good employable risks. They should not be classed with the physically handicapped or crippled, for they are capable of performing a full day's work to satisfaction despite their diabetes.

TYPES OF DIABETICS

Diabetics seeking employment naturally fall into two groups. One is composed of the mild diabetics who require no insulin for the control of their disease. The employment of these people presents no special difficulty.

The other group includes more severe diabetics who require insulin and a carefully regulated diet. This group itself is divided into two very important subgroups: the well-controlled and well-regulated patient, and the uncooperative and poorly-regulated patient.

The latter subgroup, composed of poorly-controlled, uncooperative diabetics, should be refused employment solely on the basis of their diabetic condition. This is not only because they are poor employment risks in their present condition, but also because they may develop complications which would result in increased absenteeism on their part. A prejudice against all diabetics would thus be created in the mind of the employer.

When it is said that a diabetic is a good employment risk, reference is made to the well-controlled, well-regulated diabetic who keeps himself constantly under medical supervision. These people should prove to be quite acceptable employees, as the experience of hundreds of companies employing such diabetics indicates. Indeed, because they are self-disciplined and well-balanced individuals, they often become outstanding workers in whatever positions they occupy.

SUGGESTED STANDARDS FOR THE EMPLOYMENT OF DIABETICS

The Committee would like to suggest the following standards and procedures for diabetics seeking employment and for employers planning to hire diabetics:

1. A diabetic seeking employment should be required to present a note from his physician or clinic to the plant physician or the personnel manager, stating that he is a controlled diabetic and is examined at regular intervals.
2. Diabetics are capable of performing any type of work for which they are physically, mentally and educationally equipped. Those diabetics who are taking large doses of insulin should not, however, be assigned work in which hypoglycemic attacks might result in injury to themselves and others.
3. An effort should be made to see that diabetics work the same hours on a steady shift; or, if they must work on a rotating schedule, that they avoid the "graveyard" shift from midnight to 8 a.m. This is the only concession in terms of hours that a well-controlled diabetic should ask.
4. Wherever diabetics are employed, it is often wise to inform certain key people in labor and management organizations, as well as the plant physician and personnel managers, as to the nature of diabetes and the possibility of coma or insulin reactions. (This is not always a necessary procedure, since in some instances it may create prejudice against the diabetics. The decision as to the advisability of indoctrinating key plant personnel on the problem should usually be left to the plant physician or in the absence of such a physician the personnel manager.)

   On the national scale, excellent liaison has been established by the American Diabetes Association's Committee on Employment with the top level of the three large labor organizations in this country, the Congress of Industrial Organizations, the American Federation of Labor, and the Railroad Brotherhoods, and this cooperation can unquestionably be extended down through the ranks if it is found necessary.
5. Diabetics should carry cards or tags identifying their condition at all times, particularly when on the job.
6. The plant physician can save time for the company and also help the employee by performing blood sugar and urine examinations, whenever the patient's usual laboratory facilities are available only during working hours. Ordinarily, of course, this should be done only after consultation with the family physician.
7. A complete physical examination of each diabetic should be made regularly, at least once a year.
8. A plant physician is within his rights if he reassigns a diabetic employee to other work whenever the arising of new complications creates new risks for himself or for other employees.
9. The diabetic requiring insulin should be considered controlled if the fasting blood sugar is not below normal limits and not above 150 mg. per 100 cc. by Folin Wu method and the blood sugar three hours after a meal is not higher than 250 mg. per 100 cc. by the Folin Wu method and if the patient is under regular medical supervision. Although these or more nearly normal blood sugar levels are desirable, greater hyperglycemia alone, if not extreme or habitual, need not be considered a disqualification for employment in those cases where the patient's personal physician and the industrial physician both feel that other limits should be observed.

These criteria are presented as a generalized guide for the employment of diabetics. Specific plant standards should be established by the individual company's medical department whenever advisable. The standards given herewith do not necessarily represent recommendations for diabetic treatment of individual patients by the American Diabetes Association.

A brochure containing recommended standards for the employment of diabetics approved by the American Diabetes Association should be prepared for distribution through the Industrial Hygiene Foundation and other organizations. This brochure should be made easily available to all employers.

The Committee on Employment of the American Diabetes Association is willing to act at any time in an advisory capacity with management and/or labor regarding this program.

CHESTER COGGESHALL — THOMAS P. SHARKEY
FREDERICK G. HELWIG — HUGH L. C. WILKERSON
WARREN F. DRAPER (*by invitation*)
VERNE K. HARVEY (*by invitation*)
C. RICHARD WALMER (*by invitation*)
JOSEPH T. BEARDWOOD, JR., *Chairman*

ASSOCIATION NEWS

THE TWELFTH ANNUAL MEETING

The June 1952 meeting of the American Diabetes Association in Chicago was the largest and most successful in its history. Members who registered numbered 325, a greater number than ever before. There were 102 guests, for a total of 427 registrants. Of these, 267 attended the Annual Banquet.

In addition, 38 physicians who attended the meeting as guests of the Association indicated their interest in becoming members. Inasmuch as the strength of our Association resides in the numbers as well as the quality of its membership, it is highly significant that so many non-member physicians stated that they would like to join the group. It is a sign of our organizational good health.

The panel discussions were particularly popular and successful this year. These discussions were first held during the Eleventh Annual Meeting last year, when three panels were held in succession. This year the three panels met concurrently; despite the fact that this meant that no doctor could attend more than one panel, the registered attendance was 274, a splendid attendance record.

The Banquet Session featured several important and unusually interesting events, including the presidential address by Dr. Arthur R. Colwell, the special award to Professor Charles H. Best, presented by Dr. Joslin, the presentation of the Banting Memorial Medal to Professor R. R. Bensley by Dr. Colwell, and finally the presentation of the Banting Memorial Medal to Dr. Colwell by Dr. Lester J. Palmer, past president.

In all, the Twelfth was unquestionably the best annual meeting the Association has yet held, thanks to the unsparing efforts of the President, and the chairman and members of the Committee on Scientific Programs.

PRIZE OFFERED FOR PAPER ON DIABETES

A prize for a paper on diabetes is offered to *medical students* and *interns* by the American Diabetes Association.

Candidates may select any subject related to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

Manuscripts must be submitted on or before April 1, 1953. A prize will be awarded to the writer of the paper that is judged best by the Editorial Board of DIABETES: The Journal of the American Diabetes Association, taking into consideration the value of the material and the method of presentation.

For additional information, write to DIABETES, American Diabetes Association, Inc., 11 West 42nd Street, New York 36, N. Y.

POSTGRADUATE COURSE IN DIABETES AND BASIC METABOLIC PROBLEMS

The first formal postgraduate course ever conducted independently by the American Diabetes Association is to be given January 19, 20, and 21, 1953 at Toronto, Canada, according to plans developed by the Association's Committee on Postgraduate Education, of which Edward L. Bortz, M.D., is Chairman. The course will be held both for members of the Association and also for other members of the medical profession.

Charles H. Best, M.D., Director of the Banting and Best Department of Medical Research and the Department of Physiology at the University of Toronto will be the Director of the Course. Associated with him will be other members of the staff of the University

of Toronto. Ray F. Farquharson, M.D., Professor of Medicine, will be Clinical Director, and Andrew L. Chute, M.D., Professor Pediatrics, will be Associate Clinical Director.

The course is open to physicians interested in advanced study of clinical medicine and basic medical sciences related to diabetes. Details about the course can be secured from the National Office of the American Diabetes Association, Inc., 11 West 42nd Street, New York 36, New York.

FIRST INTERNATIONAL CONGRESS INTERNATIONAL DIABETES FEDERATION

At the time of going to press, the National Office had found that 26 Americans and Canadians had attended the [illegible]tioned Congress at Leiden, The Netherlands, July [illegible]. At least eight of these men read papers at the scie[illegible]ions.

As pre[illegible]nounced, part of the program dealt with the soci[illegible]economic problems of the diabetic, including such [illegible]as education of the diabetic patient, quack me[illegible], travelling difficulties, and so forth. Among scientific [illegible]read were reports on this country's Diabetes Detection and Education programs.

Further details on the papers and on the Congress itself will appear in a future issue of DIABETES.

REQUESTS FOR RESEARCH GRANTS

According to the National Institutes of Health of the U. S. Public Health Service, applications for Federal medical research grants this year are higher than ever before in the history of the grants program. Applications for a total of $16,084,072 were presented to the Institutes during the early part of the year, with more coming in. For grants from the Institute for Arthritis and Metabolic Diseases alone, 97 applications involving requests for $1,077,139, have been received.

Action on these applications by the Advisory Councils of the National Institutes will not be announced until mid-August.

OBITUARY

James A. Bradley, M.D., of St. Petersburg, Florida, member of the American Diabetes Association since August 1941, died April 16, 1952, at the age of 52. He was on a vacation cruise to the Virgin Islands when he died, having recently retired from practice because of ill health.

Dr. Bradley was a native of Jacksonville, but attended schools in Florence, South Carolina. He obtained his medical degree from the University of Pennsylvania School of Medicine in 1927, and in 1929 was chief resident physician at Babies' Hospital in Philadelphia. Thereafter he served as assistant professor of medicine at the medical school of the University of Texas in Galveston; for one year as a medical missionary in India; and finally as Assistant Professor of Medicine at Louisiana State University Medical Center in New Orleans. Then in 1935 he took up private practice in Florence, moving in 1939 to St. Petersburg, where he remained till the end of his life.

During the war Dr. Bradley was a lieutenant commander for two years, and for one year of that time was stationed at a base hospital in Trinidad. He was a member of the American College of Physicians, The American Board of Internal Medicine, the American Medical Society, and at the time of his death was affiliated with the Mound Park Hospital.

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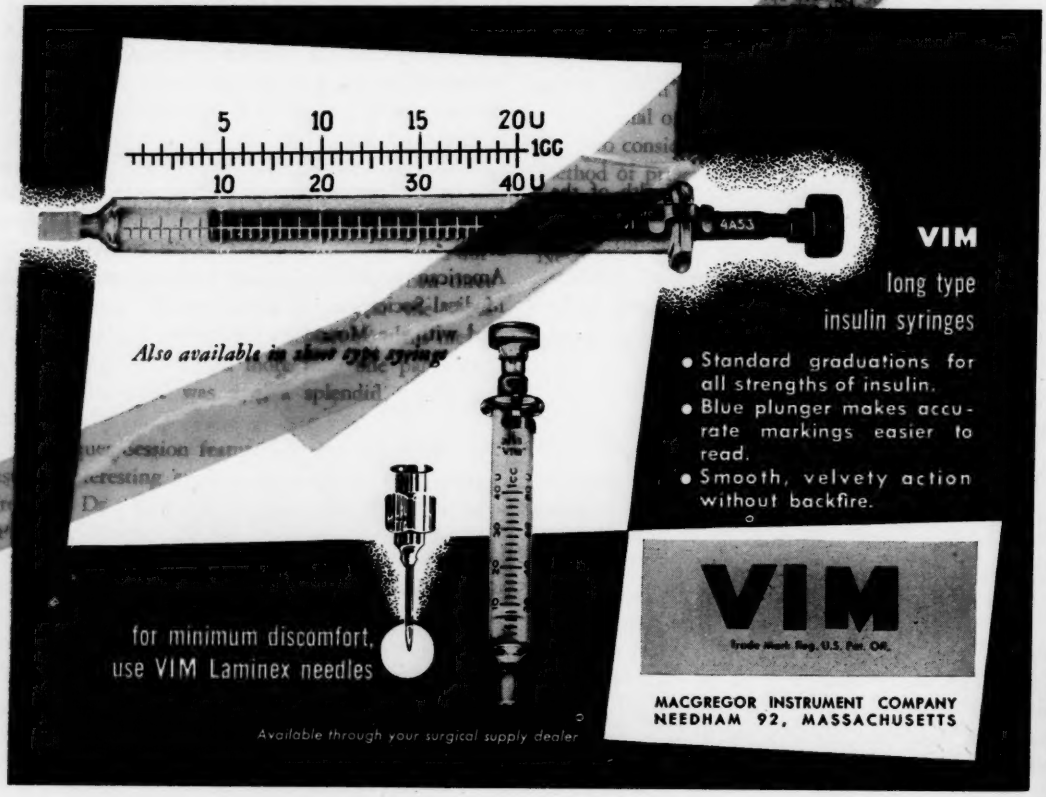

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